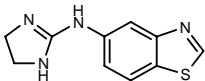


ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

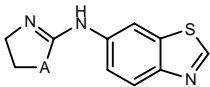
255396

N-(Benzothiazol-5-yl)-N-(4,5-dihydro-1H-imidazol-2-yl)amine



C10-H10-N4-S; Mol wt: 218.28

ACTION – Potent and selective human α_2 -adrenoceptor agonist, as demonstrated in radioligand binding studies by pK_i values of 8.43, 8.34 and 7.69, respectively, for human α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors versus 6.73, 6.15 and 6.15, respectively, for human α_{1A} -, α_{1B} - and α_{1C} -adrenoceptors; agonist activity at α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors was measured by the ability to inhibit forskolin-stimulated cAMP synthesis in stably transfected cells (pEC_{50} = 7.91, 7.99 and 9.22, respectively). Claimed for the treatment of pain, for use as an anesthetic premedication and for lowering intraocular pressure. Other specifically claimed indole and benzothiazole compounds are:



Compound	A	Formula
255929	NH	C ₁₀ H ₁₀ N ₄ S
255930	S	C ₁₀ H ₉ N ₃ S ₂

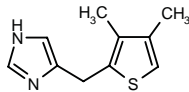
SOURCE – Synaptic.

REFERENCES

1. Jeon, Y.T. and Gluchowski, C. (Synaptic Pharm. Corp.) 5- and 6-(2-imidazolin-2-ylamino) and -(2-thiazolin-2-ylamino)-benzothiazoles as α_2 adrenergic ligands. US 5677321, WO 9731636.

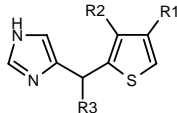
256207

4-(3,4-Dimethylthien-2-ylmethyl)-1H-imidazole



C10-H12-N2-S; Mol wt: 192.28

ACTION – Analgesic agent, an α_2 -adrenoceptor agonist with high affinity for α_{2D} -receptors from rat spinal cord (K_i = 0.17 nM). *In vivo* analgesic activity was determined by measuring inhibition of acetylcholine bromide-induced abdominal constriction in mice (100% at 30 mg/kg p.o.). Other representative compounds within this series of 4-[(thien-2-yl)methyl]imidazole derivatives include the following:



Compound	R1	R2	R3	Formula
257511	H	Me	H	C ₉ H ₁₀ N ₂ S
257512	H	Me	Me	C ₁₀ H ₁₂ N ₂ S
257513	H	Br	H	C ₈ H ₇ BrN ₂ S
257514	H	Br	Me	C ₉ H ₉ BrN ₂ S
257515	Me	Me	Me	C ₁₁ H ₁₄ N ₂ S
257516	Br	Br	H	C ₈ H ₆ Br ₂ N ₂ S
257517	Br	Br	Me	C ₉ H ₈ Br ₂ N ₂ S
257518	Br	H	H	C ₈ H ₇ BrN ₂ S

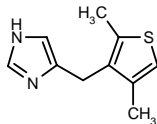
SOURCE – Ortho.

REFERENCES

1. Boyd, R.E. et al. (Ortho Pharm. Corp.) 4-[(Thien-2-yl)methyl]imidazole derivs. having α_2 -adrenoceptor agonistic activity. WO 9735857.

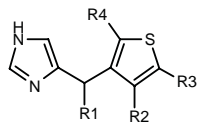
256208

4-(2,4-Dimethylthien-3-ylmethyl)-1H-imidazole



C10-H12-N2-S; Mol wt: 192.28

ACTION – Analgesic agent with α_{2D} -adrenoceptor-agonist activity ($K_i = 0.10$ nM against [3H]-*p*-aminoclonidine binding in rat cortex membranes). Antinociceptive activity was demonstrated in the mouse acetylcholine bromide-induced abdominal constriction assay (100% inhibition at 30 mg/kg p.o.). A representative compound from a series of 4-[(thien-3-yl)methyl]imidazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
257501	H	H	H	Me	C ₉ H ₁₀ N ₂ S
257502	H	Me	H	H	C ₉ H ₁₀ N ₂ S
257503	Me	Me	H	H	C ₁₀ H ₁₂ N ₂ S
257504	Et	Me	H	H	C ₁₁ H ₁₄ N ₂ S
257505	H	H	Me	Me	C ₁₀ H ₁₂ N ₂ S
257507	H	H	Et	Et	C ₁₂ H ₁₆ N ₂ S
257508	H	H	H	Et	C ₁₀ H ₁₂ N ₂ S
257509	H	Et	H	H	C ₁₀ H ₁₂ N ₂ S
257510	Me	Et	H	H	C ₁₁ H ₁₄ N ₂ S

SOURCE – Ortho.

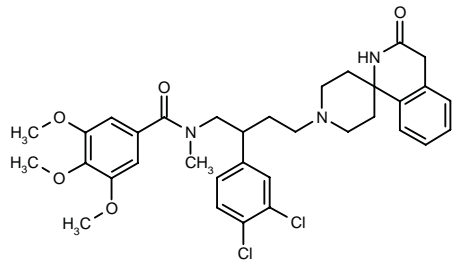
REFERENCES

1. Boyd, R.E. et al. (Ortho Pharm. Corp.) 4-[(Thien-3-yl)methyl]imidazole derivs. having α_2 -adrenoceptor agonistic activity. WO 9735858.

YM-44778*

257645
234742 (as fumarate)

N-[2-(3,4-Dichlorophenyl)-4-[3-oxo-1,2,3,4-tetrahydrospiro[isoquinoline-1,4'-piperidin]-1'-yl]butyl]-3,4,5-trimethoxy-*N*-methylbenzamide



C34-H39-Cl2-N3-O5; Mol wt: 640.61

ACTION – Dual tachykinin NK₁ and NK₂ receptor antagonist, as demonstrated in binding assays ($IC_{50} = 18$ and 16 nM, respectively), potentially useful in the treatment of pain, respiratory, inflammatory and CNS disorders.

SOURCE – Yamanouchi.

REFERENCES

1. Kubota, H. et al. (Yamanouchi Pharm. Co., Ltd.) *Spiro cpd. and medicinal compns. thereof*. WO 9528389.

2. Kubota, H. et al. *Synthesis and structure-activity relationships of spiro-substituted piperidines as NK1-NK2 dual antagonists*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-17.

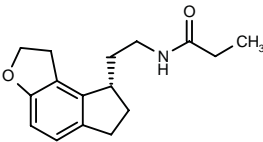
*Identified compound **234742** (see **230611**) Annu Drug Data Rep 1996, 18(5): 403.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

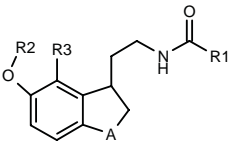
255673

(*S*)-*N*-[2-(2,6,7,8-Tetrahydro-1 *H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide

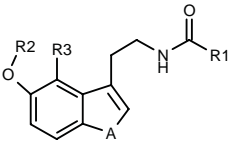


C16-H21-N-O2; Mol wt: 259.35

ACTION – Melatonin agonist with high binding affinity for the melatonin receptor ($IC_{50} = 0.048$ nM against 2-[^{125}I]-iodomelatonin binding in forebrain homogenates of 7-day-old chickens). Claimed for use in the treatment of various disorders associated with melatonin activity such as sleep disorders. Within this series of tricyclic compounds, the following are also included:

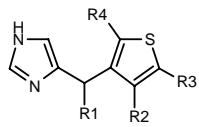


Compound	R1	R2	R3	A	Formula
256515	Me	-(CH2)2-		CH2	C ₁₅ H ₁₉ NO ₂
256516	Et	-(CH2)2-		CH2	C ₁₆ H ₂₁ NO ₂
256520	Et	-(CH2)3-		NH	C ₁₆ H ₂₂ N ₂ O ₂
256521	Pr	-(CH2)3-		NH	C ₁₇ H ₂₄ N ₂ O ₂
256522	Pr	-(CH2)2-		CH2	C ₁₇ H ₂₃ NO ₂



Compound	R1	R2	R3	A	Formula
256517	Me	-(CH2)3-		NH	C ₁₅ H ₁₉ N ₂ O ₂
256518	Et	-(CH2)3-		NH	C ₁₆ H ₂₀ N ₂ O ₂
256519	Pr	-(CH2)3-		NH	C ₁₇ H ₂₂ N ₂ O ₂
256523	Me	-(CH2)2-		CH2	C ₁₅ H ₁₇ NO ₂
256524	Et	-(CH2)2-		CH2	C ₁₆ H ₁₉ NO ₂
256525	Pr	-(CH2)2-		CH2	C ₁₇ H ₂₁ NO ₂

ACTION – Analgesic agent with α_{2D} -adrenoceptor-agonist activity ($K_i = 0.10$ nM against [3H]-*p*-aminoclonidine binding in rat cortex membranes). Antinociceptive activity was demonstrated in the mouse acetylcholine bromide-induced abdominal constriction assay (100% inhibition at 30 mg/kg p.o.). A representative compound from a series of 4-[(thien-3-yl)methyl]imidazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
257501	H	H	H	Me	C ₉ H ₁₀ N ₂ S
257502	H	Me	H	H	C ₉ H ₁₀ N ₂ S
257503	Me	Me	H	H	C ₁₀ H ₁₂ N ₂ S
257504	Et	Me	H	H	C ₁₁ H ₁₄ N ₂ S
257505	H	H	Me	Me	C ₁₀ H ₁₂ N ₂ S
257507	H	H	Et	Et	C ₁₂ H ₁₆ N ₂ S
257508	H	H	H	Et	C ₁₀ H ₁₂ N ₂ S
257509	H	Et	H	H	C ₁₀ H ₁₂ N ₂ S
257510	Me	Et	H	H	C ₁₁ H ₁₄ N ₂ S

SOURCE – Ortho.

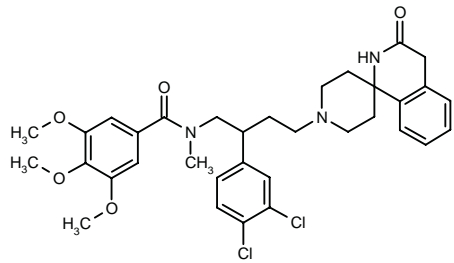
REFERENCES

1. Boyd, R.E. et al. (Ortho Pharm. Corp.) 4-[(Thien-3-yl)methyl]imidazole derivs. having α_2 -adrenoceptor agonistic activity. WO 9735858.

YM-44778*

257645
234742 (as fumarate)

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C34-H39-Cl2-N3-O5; Mol wt: 640.61

ACTION – Dual tachykinin NK₁ and NK₂ receptor antagonist, as demonstrated in binding assays ($IC_{50} = 18$ and 16 nM, respectively), potentially useful in the treatment of pain, respiratory, inflammatory and CNS disorders.

SOURCE – Yamanouchi.

REFERENCES

1. Kubota, H. et al. (Yamanouchi Pharm. Co., Ltd.) *Spiro cpd. and medicinal compsn. thereof*. WO 9528389.

2. Kubota, H. et al. *Synthesis and structure-activity relationships of spiro-substituted piperidines as NK1-NK2 dual antagonists*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-17.

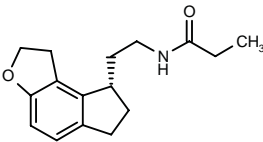
*Identified compound **234742** (see **230611**) Annu Drug Data Rep 1996, 18(5): 403.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

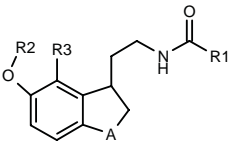
255673

(*S*)-*N*-[2-(2,6,7,8-Tetrahydro-1 *H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide

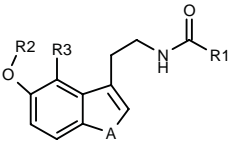


C16-H21-N-O2; Mol wt: 259.35

ACTION – Melatonin agonist with high binding affinity for the melatonin receptor ($IC_{50} = 0.048$ nM against 2-[^{125}I]-iodomelatonin binding in forebrain homogenates of 7-day-old chickens). Claimed for use in the treatment of various disorders associated with melatonin activity such as sleep disorders. Within this series of tricyclic compounds, the following are also included:



Compound	R1	R2	R3	A	Formula
256515	Me	-(CH2)2-	CH2		C ₁₅ H ₁₉ NO ₂
256516	Et	-(CH2)2-	CH2		C ₁₆ H ₂₁ NO ₂
256520	Et	-(CH2)3-	NH		C ₁₆ H ₂₂ N ₂ O ₂
256521	Pr	-(CH2)3-	NH		C ₁₇ H ₂₄ N ₂ O ₂
256522	Pr	-(CH2)2-	CH2		C ₁₇ H ₂₃ NO ₂



Compound	R1	R2	R3	A	Formula
256517	Me	-(CH2)3-	NH		C ₁₅ H ₁₉ N ₂ O ₂
256518	Et	-(CH2)3-	NH		C ₁₆ H ₂₀ N ₂ O ₂
256519	Pr	-(CH2)3-	NH		C ₁₇ H ₂₂ N ₂ O ₂
256523	Me	-(CH2)2-	CH2		C ₁₅ H ₁₇ NO ₂
256524	Et	-(CH2)2-	CH2		C ₁₆ H ₁₉ NO ₂
256525	Pr	-(CH2)2-	CH2		C ₁₇ H ₂₁ NO ₂

SOURCE – Takeda.

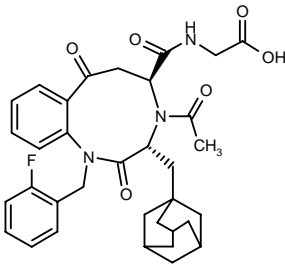
REFERENCES

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ANXIOLYTICS

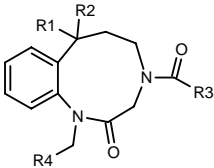
255668

(3*R*,5*S*)-*N*-[4-Acetyl-3-(1-adamantylmethyl)-1-(2-fluorobenzyl)-2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-1,4-benzodiazonin-5-ylcarbonyl]glycine



C34-H38-F-N3-O6; Mol wt: 603.69

ACTION – Cholecystokinin B (CCK_B)/gastrin receptor antagonist with a p*K*_i of 7.0 in a binding assay using mouse cortical homogenates, displaying 100-fold greater selectivity for these receptors compared to CCK_A receptors (p*K*_i = 5.0 using guinea pig pancreas homogenates). Potentially useful for the treatment of anxiety, appetite disorders, pancreatitis, etc. A representative compound from a series of benzodiazonine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
256645	-O-		3,4-(Cl)2-PhNH	t-BuOCO	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₅
256646	H	Me	2-Naph-NH	Ph	C ₃₀ H ₂₉ N ₃ O ₂
256647	-O-		Me	2-Cl-Ph	C ₃₅ H ₃₉ ClN ₂ O ₆

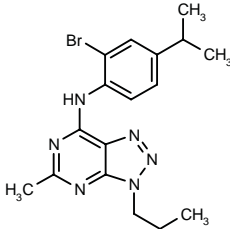
SOURCE – James Black Found.

REFERENCES

1. Kalindjian, S.B. et al. (James Black Found., Ltd.) *Benzodiazonine derivs. binding to cholecystokinin or gastrin receptors.* WO 9732860.

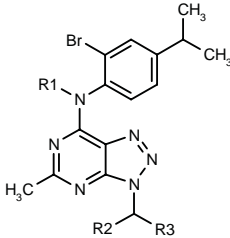
256172

N-(2-Bromo-4-isopropylphenyl)-*N*-(5-methyl-3-propyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-yl)amine



C17-H21-Br-N6; Mol wt: 389.30

ACTION – Agent for the treatment of anxiety and depression with corticotropin-releasing factor (CRF)-antagonist activity. A specifically claimed compound from a wide series of arylamino fused pyridines and pyrimidines, wherein the following are also included:



Compound	R1	R2	R3	Formula
257570	Et	Pr	H	C ₂₀ H ₂₇ BrN ₆
257571	Et	cyclopropyl	H	C ₂₀ H ₂₅ BrN ₆
257572	H	(<i>S</i>)-CH ₂ Ph	CH ₂ OMe	C ₂₄ H ₂₇ BrN ₆ O
257573	H	Bu	Et	C ₂₁ H ₂₉ BrN ₆

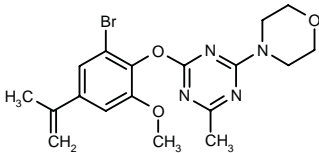
SOURCE – DuPont Merck.

REFERENCES

1. Bakthavatchalam, R. et al. (The Du Pont Merck Pharm. Co.) *Arylamino fused pyridines and pyrimidines.* WO 9735539.

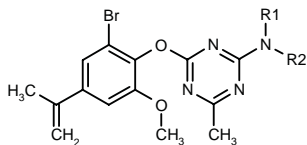
256185

2-[2-Bromo-6-methoxy-4-(1-methylvinyl)phenoxy]-4-methyl-6-(4-morpholinyl)-1,3,5-triazine



C18-H21-Br-N4-O3; Mol wt: 421.29

ACTION – Anxiolytic agent and antidepressant that acts by virtue of its corticotropin-releasing factor (CRF)-antagonist activity. Within this series of specifically claimed aryl-oxy- and arylthio-substituted pyrimidine and triazine derivatives, the following are also included:



Compound	R1	R2	Formula
258194	CH2CH2OMe	CH2CH2OMe	C ₂₀ H ₂₇ BrN ₄ O ₄
258195	cyclopropyl-CH2	Pr	C ₂₁ H ₂₇ BrN ₄ O ₂
258196	-(CH2)6-		C ₂₀ H ₂₅ BrN ₄ O ₂
258197	Et	Et	C ₁₈ H ₂₃ BrN ₄ O ₂
258198	Bu	Et	C ₂₀ H ₂₇ BrN ₄ O ₂
258199	-CH2CH2SCH2CH2-		C ₁₈ H ₂₁ BrN ₄ O ₂ S

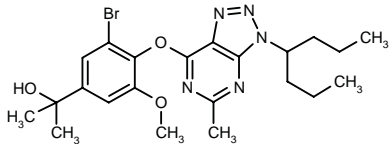
SOURCE – DuPont Merck.

REFERENCES

1. Chorvat, R.J. and Rajagopalan, P. (The Du Pont Merck Pharm. Co.) Aryloxy- and arylthio-subst. pyrimidines and triazines and derivs. thereof. WO 9735580.

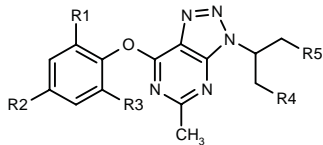
256201

1-[3-Bromo-5-methoxy-4-[5-methyl-3-(1-propylbutyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-yloxy]phenyl]-1,1-dimethylmethanol

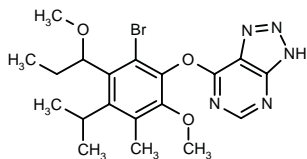


C22-H30-Br-N5-O3; Mol wt: 492.41

ACTION – Anxiolytic agent and antidepressant that acts by virtue of its corticotropin-releasing factor (CRF)-antagonist activity. Within this series of specifically claimed aryl-oxy- and arylthio-fused pyridine and pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	R4=R5	Formula
257519	Br	C(Me)=CH2	OMe	Me	C ₂₂ H ₂₈ BrN ₅ O ₂
257520	Br	i-Pr	OMe	Me	C ₂₂ H ₃₀ BrN ₅ O ₂
257521	Me	Me	Me	H	C ₁₉ H ₂₅ N ₅ O



258200: C19-H24-Br-N5-O3

SOURCE – DuPont Merck.

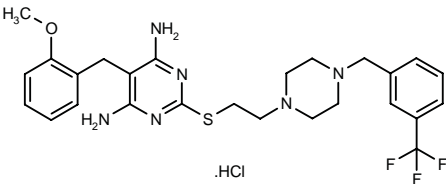
REFERENCES

1. Rajagopalan, P. et al. (The Du Pont Merck Pharm. Co.) Aryloxy- and arylthio-fused pyridines and pyrimidines and derivs. WO 9735846.

EGIS-9933

257395

5-(2-Methoxybenzyl)-2-[2-[4-[3-(trifluoromethyl)benzyl]-1-piperazinyl]ethylsulfanyl]pyrimidine-4,6-diamine hydrochloride



C26-H31-F3-N6-O-S.HCl; Mol wt: 569.09

ACTION – Anxiolytic agent with good selectivity for 5-HT_{2C} receptors. The compound inhibited mCPP-induced hyperthermia and hypomotility in rats and demonstrated significant activity in rodent models of anxiety such as the elevated plus maze test, the social interaction test and the Vogel conflict test. Unlike diazepam, at doses up to 100 mg/kg it did not inhibit spontaneous motor activity in mice or rats.

SOURCE – Egis.

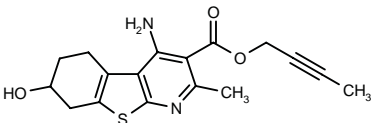
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2. Gacslyi, I. et al. Anxiolytic effect of the new 5-HT_{2C} selective compound EGIS-9933 in rats. Soc Neurosci Abst 1997, 23(Part 2): Abst 835.9.

SB-205384*

197689

(±)-4-Amino-7-hydroxy-2-methyl-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-b]pyridine-3-carboxylic acid 2-butyryl ester



C17-H18-N2-O3-S; Mol wt: 330.40

ACTION – GABA_A receptor modulator shown in electrophysiological studies in cultured cerebellar granule cells to markedly prolong the decay of GABA-activated current upon removal of agonist, with less effect on peak GABA-activated current. This is in contrast to many existing GABA_A receptor modulators which potentiate GABA-activated currents. Potentially useful as an anxiolytic agent, for the treatment of sleep disorders, depression and epilepsy, without the side effects typical of benzodiazepines.

SOURCE – SmithKline Beecham.

REFERENCES

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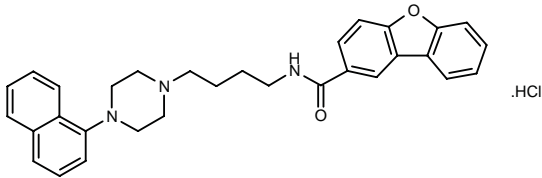
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*Identified compound **197689** (see **195367**) Annu Drug Data Rep 1995, 15(8): 703.

ANTIPSYCHOTIC DRUGS

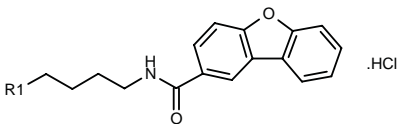
255620

N-[4-[4-(1-Naphthyl)piperazin-1-yl]butyl]dibenzofuran-2-carboxamide hydrochloride

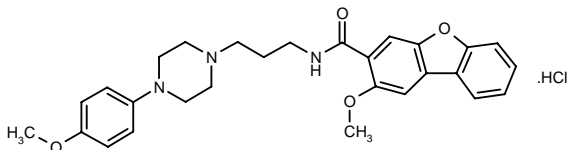


C31-H31-N3-O2.HCl; Mol wt: 514.07

ACTION – Agent for the treatment of affective disorders such as schizophrenia, depression and Alzheimer’s disease, and movement disorders such as parkinsonism, a dopamine receptor antagonist with high and selective affinity for dopamine D₃ receptors (K_i = 1.3 nM in rat striatal homogenates) versus D₂ receptors (K_i = 201 nM in rat striatal homogenates). Other specifically claimed N-aminoalkyldibenzofurancarboxamides include the following:



Compound	R1	Formula
256571	4-[2,3-(Cl)2-Ph]-1-Piz	C27H27Cl2N3O2.HCl
256572	4-(3-Cl-2-Me-Ph)-1-Piz	C28H30ClN3O2.HCl
256573	4-[2,3-(Me)2-Ph]-1-Piz	C29H33N3O2.HCl
256574	4-(2-MeO-Ph)-1-Piz	C28H31N3O3.HCl
256575	4-Ph-1,2,3,6-tetrahydro-1-Pyr	C28H28N2O2.HCl



256576: C28-H31-N3-O4.HCl

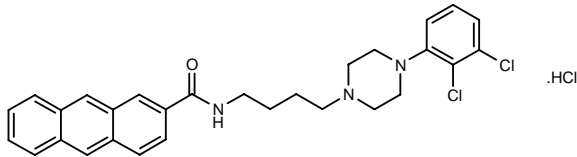
SOURCE – Neurogen.

REFERENCES

1. Yuan, J. and Chen, X. (Neurogen Corp.) *N-Aminoalkyldibenzofurancarboxamides as dopamine receptor subtype specific ligands*. US 5710274, WO 9731916.

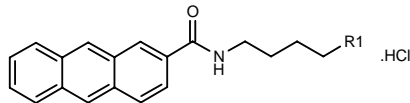
256157

N-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-anthracene-2-carboxamide hydrochloride



C29-H29-Cl2-N3-O.HCl; Mol wt: 542.93

ACTION – Agent for the treatment or prevention of neuropsychological disorders such as schizophrenia, mania, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson’s disease and motion disorders related to the use of neuroleptic agents that exhibits high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors (K_i = 7 and 1089 nM, respectively, for displacement of [³H]-YM-09151-2 binding to recombinant monkey D₃ and D₂ receptors expressed in COS cells). A representative compound from a series of specifically claimed N-aminoalkyl-2-anthracenecarboxamides, wherein the following are also included:



Compound	R1	Formula
257279	4-(1-Naph)-1-Piz	C33H33N3O.HCl
257280	4-[2,3-(Me)2-Ph]-1-Piz	C31H36N3O.HCl
257281	4-(2-Me-Ph)-1-Piz	C30H33N3O.HCl
257282	4-(2-Cl-Ph)-1-Piz	C29H30ClN3O.HCl
257283	4-(2-MeO-Ph)-1-Piz	C30H33N3O2.HCl
257284	4-(8-isoquinolyl)-1-Piz	C32H32N4O.HCl
257285	4-(3-Cl-2-Me-Ph)-1-Piz	C30H32ClN3O.HCl
257286	4-Ph-1,2,3,6-tetrahydro-1-Pyr	C30H30N2O.HCl
257287	4-(1-Naph)-1,2,3,6-tetrahydro-1-Pyr	C34H32N2O.HCl
257288	4-Ph-1-Pip	C30H32N2O.HCl

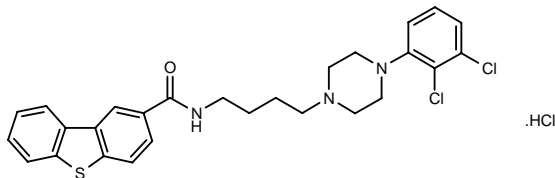
SOURCE – Neurogen.

REFERENCES

1. Yuan, J. and Chen, X. (Neurogen Corp.) *Novel N-aminoalkyl-2-anthracenecarboxamides; new dopamine receptor subtype specific ligands*. US 5703235, WO 9734884.

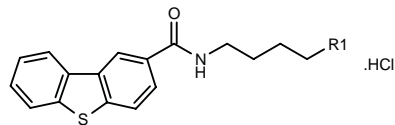
256159

N-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]dibenzothiophene-2-carboxamide hydrochloride

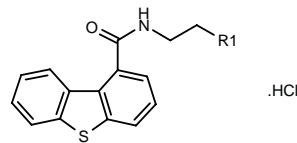


C27-H27-Cl2-N3-O-S.HCl; Mol wt: 548.96

ACTION – Agent for the treatment or prevention of neuropsychological disorders such as schizophrenia, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson’s disease and motor disorders related to the use of neuroleptic agents that exhibits high affinity and selectivity for the dopamine D₃ receptor subtype relative to the D₂ subtype (K_i = 3.5 and 285 nM, respectively, for displacement of [³H]-YM-09151-2 binding to D₃ and D₂ receptors). Other compounds from this series of specifically claimed dibenzothiophenecarboxamides include the following:



Compound	R1	Formula
257348	4-(1-Naph)-1-Piz	C ₃₁ H ₃₁ N ₃ OS.HCl
257349	4-(3-Cl-2-Me-Ph)-1-Piz	C ₂₈ H ₃₀ ClN ₃ OS.HCl
257350	4-[2,3-(Me)2-Ph]-1-Piz	C ₂₉ H ₃₃ N ₃ OS.HCl
257351	4-(2-Cl-Ph)-1-Piz	C ₂₇ H ₂₈ ClN ₃ OS.HCl
257352	4-(2-Me-Ph)-1-Piz	C ₂₈ H ₃₁ N ₃ OS.HCl
257353	4-(8-quinoliny)-1-Piz	C ₃₀ H ₃₀ N ₄ OS.HCl
257354	4-Ph-1,2,3,6-tetrahydro-1-Pyr	C ₂₈ H ₂₈ N ₂ OS.HCl



Compound	R1	Formula
257355	4-[2,3-(Cl)2-Ph]-1-Piz-CH2CH2	C ₂₇ H ₂₇ Cl ₂ N ₃ OS.HCl
257357	4-(1-Naph)-1-Piz-CH2CH2	C ₃₁ H ₃₁ N ₃ OS.HCl
257358	4-(1-Naph)-1-Piz	C ₂₉ H ₂₇ N ₃ OS.HCl

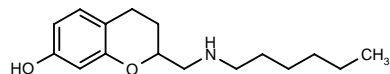
SOURCE – Neurogen.

REFERENCES

1. Yuan, J. and Chen, X. (Neurogen Corp.) *N-Aminoalkyldibenzothiophene-carboxamides; dopamine receptor subtype specific ligands.* WO 9734889.

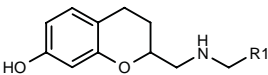
256303

2-(Hexylaminomethyl)-3,4-dihydro-2H-1-benzopyran-7-ol



C16-H25-N-O2; Mol wt: 263.38

ACTION – Antipsychotic agent reported to be free from extrapyramidal side effects, a selective dopamine autoreceptor agonist, as demonstrated by inhibition of [³H]-quinpirole binding in rat striatal brain preparations (IC₅₀ = 1.63 nM), with relatively much lower affinity for postsynaptic dopamine D₂ receptors (IC₅₀ = 313 nM against [³H]-spiroperidol binding in limbic brain preparations). In addition, it shows affinity for 5-HT_{1A} receptors (IC₅₀ = 5.76 nM) and relatively low affinity for α₁-adrenoceptors (IC₅₀ = 221 nM). Also potentially useful for the treatment of other dopaminergic disorders such as Parkinson’s disease, Tourette’s syndrome, alcohol abuse and drug addiction. Within this series of specifically claimed chroman-2-ylmethylamino derivatives, the following are also included:



Compound	R1	Formula
258017	Pr	C ₁₄ H ₂₁ NO ₂
258018	Et	C ₁₃ H ₁₉ NO ₂
258019	i-Pr	C ₁₄ H ₂₁ NO ₂
258020	i-Bu	C ₁₅ H ₂₃ NO ₂
258021	CH2CH2OH	C ₁₃ H ₁₉ NO ₃
258022	cyclohexyl	C ₁₇ H ₂₅ NO ₂

SOURCE – American Home Products.

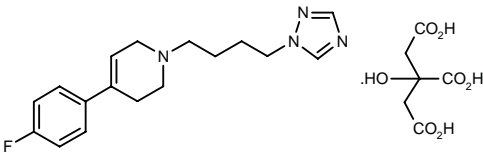
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E-5842

256549

4-(4-Fluorophenyl)-1-[4-(1,2,4-triazol-1-yl)butyl]-1,2,3,6-tetrahydropyridine citrate



C17-H21-F-N4.C6-H8-O7; Mol wt: 492.50

ACTION – Atypical antipsychotic agent with high affinity for σ₁-receptors (K_i = 4 nM) and moderate or low affinity for other receptors (K_i = 89, 116, 119 and 220 nM, respectively, for α_{2B}-, α_{1B}- and α_{1A}-adrenoceptors and σ₂-receptors). It increased dopamine release in the prefrontal cortex and striatum in rats administered a dose of 20 mg/kg i.p. and induced FOS protein expression in the nucleus accumbens and prefrontal cortex at a dose of 20 mg/kg s.c. The compound blocked apomorphine-induced climbing in mice (ED₅₀ = 7.7 mg/kg i.p.), mescaline-induced scratching in mice (ED₅₀ = 3.4 mg/kg i.p., 7 mg/kg p.o.), amphetamine-induced hyperactivity in mice and rats (ED₅₀ = 5 and 3.8 mg/kg i.p., respectively) and the conditioned avoidance response in rats (ED₅₀ = 8.1 mg/kg p.o., 5.5 mg/kg i.p.). It was also active in the social interaction test in rats (minimum effective dose = 0.01 mg/kg i.p.), but did not induce catalepsy in rats (ED₅₀ > 80 mg/kg s.c.). This profile suggests efficacy against both positive and negative symptoms of schizophrenia and a low liability for extrapyramidal side effects.

SOURCE – Esteve.

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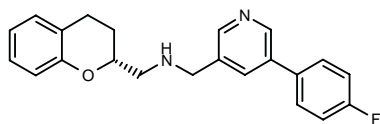
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EMD-128130

257398

(–)-(R)-N-(3,4-Dihydro-2H-1-benzofuran-2-ylmethyl)-N-[5-(4-fluorophenyl)-3-pyridylmethyl]amine



C22-H21-F-N2-O; Mol wt: 348.42

ACTION – Atypical antipsychotic agent with dopamine D₂ receptor-antagonist and 5-HT_{1A} receptor-agonist properties; it gave IC₅₀ values in binding studies of 1, 5, 6 and 2 nM, respectively, for human dopamine D₂, D₃ and D₄ receptors and 5-HT_{1A} receptors, with no affinity for other receptors. *In vivo*, activity was demonstrated by stimulation of DOPA accumulation and inhibition of 5-HTP accumulation in rat striatum (ED₅₀ = 3 mg/kg p.o. and 1 mg/kg p.o., respectively). In behavioral models, it inhibited apomorphine-induced climbing in mice (ED₅₀ = 5 mg/kg s.c. and 20 mg/kg p.o.) and stereotyped behavior in rats (ED₅₀ = 7 mg/kg s.c. and 16 mg/kg p.o.). The compound is devoid of cataleptogenic effects at single doses of up to 30 mg/kg s.c. or 300 mg/kg p.o., and multiple doses of 100 mg/kg p.o. for 12 days, and it also reversed haloperidol-induced catalepsy (ED₅₀ = 4 mg/kg s.c., 10 mg/kg p.o.).

SOURCE – Merck KGaA.

REFERENCES

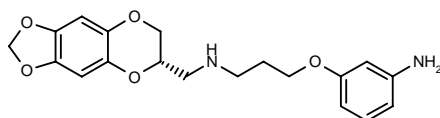
1. Böttcher, H. et al. (Merck Patent GmbH) *Amino(thio)ether derivs. as CNS active agents*. CA 2160447, EP 707007, JP 96225501.
2. Bartoszyk, G.D. et al. *Pharmacological profile of EMD 128130: A putative atypical antipsychotic with dopamine D₂ antagonistic and serotonin 5-HT_{1A} agonistic properties*. Soc Neurosci Abstr 1997, 23(Part 1): Abstr 207.5.
3. Böttcher, H. et al. *SAR for novel chromanes: Atypical neuroleptics with 5HT_{1A} agonistic and D₂ antagonistic activity*. Soc Neurosci Abstr 1996, 22(Part 2): Abstr 334.1.

WAY-127312

257394

(S)-N-[3-(3-Aminophenoxy)propyl]-6,7-dihydro-1,3-dioxolo[4,5-g][1,4]benzodioxin-6-methanamine

2(S)-[3-(3-Aminophenoxy)propylaminomethyl]-6,7-(methylenedioxy)-1,4-benzodioxane



C19-H22-N2-O5; Mol wt: 358.39

ACTION – Antipsychotic agent, a dopamine D₂ partial agonist, as demonstrated in binding, functional and behavior assays. *In vivo*, the compound reduced locomotor activity in nonhabituated mice (ED₅₀ = 0.9 mg/kg i.p.) and rats (ED₅₀ = 0.8 mg/kg i.p.), with no effect in habituated animals, and it antagonized apomorphine-induced climbing behavior (ED₅₀ = 11.4 mg/kg i.p.) and amphetamine-induced hyperactivity in mice (ED₅₀ = 1.1 mg/kg i.p.), without affecting apomorphine-induced stereotypy. It produced dose-dependent reductions in conditioned avoid-

ance (ED₅₀ = 17.4 mg/kg i.p.) and significant reversal of haloperidol-induced catalepsy in rats (ED₅₀ = 3 mg/kg s.c.), but failed to induce catalepsy in rats at up to 60 mg/kg i.p.

SOURCE – Wyeth-Ayerst.

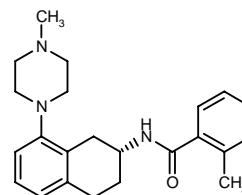
REFERENCES

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2. Marquis, K.L. et al. *Behavioral pharmacological and neurophysiological profile of a dopamine D₂ partial agonist WAY-127312*. Soc Neurosci Abstr 1997, 23(Part 1): Abstr 207.7.
3. Wasik, T. et al. *The neuropharmacological profile of the dopamine D₂ partial agonist WAY-127312*. Soc Neurosci Abstr 1997, 23(Part 1): Abstr 207.6.

ANTIDEPRESSANTS

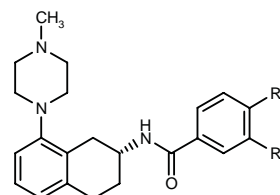
256156

2-Methyl-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-2(R)-yl]benzamide



C23-H29-N3-O; Mol wt: 363.50

ACTION – Selective, orally bioavailable 5-HT_{1D} receptor antagonist with potential in the treatment of mood disorders, anxiety, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain, hypertension, urinary incontinence, vasospasm, and for controlling the growth of tumors. A representative compound from a series of specifically claimed 1,2,3,4-tetrahydronaphthalene derivatives, wherein the following are also included:



Compound	R1	R2	Formula
257342	H	CN	C ₂₃ H ₂₆ N ₄ O
257343	H	F	C ₂₂ H ₂₆ FN ₃ O
257344	H	4-OH-Ph	C ₂₈ H ₃₁ N ₃ O ₂
257345	OPh	H	C ₂₈ H ₃₁ N ₃ O ₂

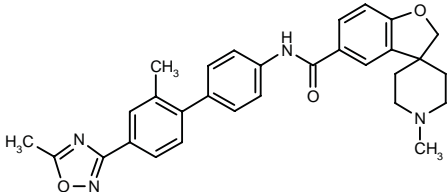
SOURCE – Astra.

REFERENCES

1. Berg, S. (Astra AB) *Substd. 1,2,3,4-tetrahydronaphthalene derivs.* WO 9734883.

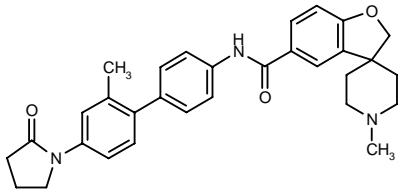
256211

N-[2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]-1'-methyl-2,3-dihydrospiro[benzofuran-3,4'-piperidine]-5-carboxamide



C30-H30-N4-O3; Mol wt: 494.59

ACTION – Antidepressant and anxiolytic agent, a 5-HT_{1B} (formerly 5-HT_{1Dβ}) receptor antagonist. Another specifically claimed azaspiro derivative is:



257491: C31-H33-N3-O3

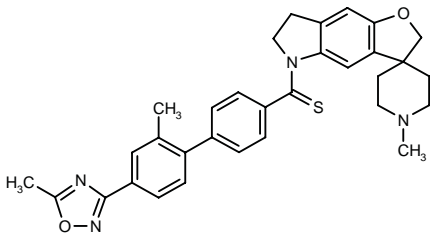
SOURCE – SmithKline Beecham.

REFERENCES

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256212

1'-Methyl-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-ylthiocarbonyl]-2,3,6,7-tetrahydro-5H-spiro[furo[2,3-f]indole-3,4'-piperidine]



C32-H32-N4-O2-S; Mol wt: 536.69

ACTION – Agent for the treatment of CNS disorders such as depression, anxiety, dementia, eating disorders and motor disorders that acts as a 5-HT_{1B} (formerly 5-HT_{1Dβ}) receptor antagonist.

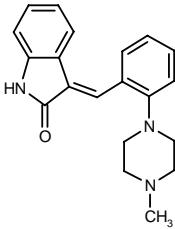
SOURCE – SmithKline Beecham.

REFERENCES

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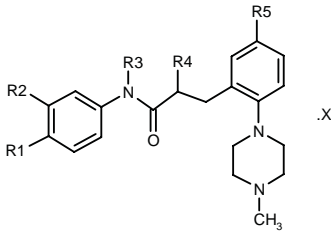
257155

3-[2-(4-Methylpiperazin-1-yl)benzylidene]-2,3-dihydro-1H-indol-2-one

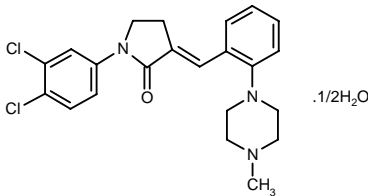


C20-H21-N3-O; Mol wt: 319.41

ACTION – A compound within a series of selective 5-HT_{1A} and/or 5-HT_{1D} receptor agonists and antagonists, potentially useful in the treatment of depression, anxiety, hypertension, eating disorders drug abuse, migraine, pain, cognition disorders and gastrointestinal motility disorders. Other compounds from this series of lactam derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
257693	F	F	-(CH2)2-	H			C ₂₂ H ₂₅ F ₂ N ₃ O
257694	H	H	-(CH2)2-	H			C ₂₂ H ₂₇ N ₃ O
257695	CF ₃	H	-(CH2)2-	H	HCl .H ₂ O		C ₂₃ H ₂₆ F ₃ N ₃ O.HCl.H ₂ O
257696	Cl	Cl	-(CH2)3-	H	HCl		C ₂₃ H ₂₇ Cl ₂ N ₃ O.HCl
257697	Cl	Cl	-(CH2)3-	F	HCl		C ₂₃ H ₂₆ Cl ₂ FN ₃ O.HCl



257692: C22-H23-Cl2-N3-O.1/2H2O

SOURCE – Pfizer.

REFERENCES

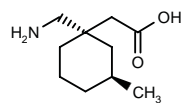
1. Howard, H.R. (Pfizer, Inc.) *Benzyl(idene)-lactam derivs., their preparation and their use as elective (ant)agonists of 5-HT_{1A} and/or 5-HT_{1D} receptors.* WO 9736867.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

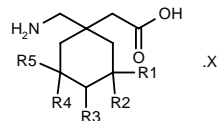
255699

[1*S*-(1 α ,3 β)]-2-[1-(Aminomethyl)-3-methylcyclohexyl]-acetic acid

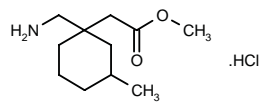


C10-H19-N-O2; Mol wt: 185.27

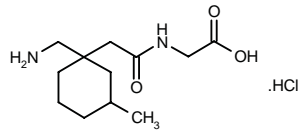
ACTION – Anticonvulsant and neuronal injury inhibitor, also claimed for the treatment of depression and anxiety; it binds to the calcium channel $\alpha_2\delta$ subunit (IC_{50} = 0.030 μ M using [3 H]-gabapentin as the radioligand and porcine brain tissue) and is expected to possess activity similar to gabapentin. It appears to act as a GABA agonist or GABA mimetic. Other specifically claimed substituted cyclic amino acids include the following:



Compound	R1	R2	R3	R4=R5	Isomer	Formula
256810	Me	Me	H	H	racemic	C ₁₁ H ₂₁ NO ₂
256811	Me	Me	H	Me		C ₁₃ H ₂₅ NO ₂
256812	H	H	Me	H		C ₁₀ H ₁₉ NO ₂
256813	Me	H	H	H	1 <i>R</i> -(1 α ,3 β)	C ₁₀ H ₁₉ NO ₂
256814	Me	H	H	H		C ₁₀ H ₁₉ NO ₂
256815	H	H	<i>t</i> -Bu	H		C ₁₃ H ₂₅ NO ₂
256816	H	H	Me	H	cis	C ₁₀ H ₁₉ NO ₂



256817: C11-H21-N-O2.HCl



256819: C12-H22-N2-O3.HCl

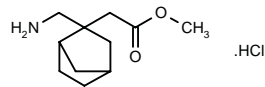
SOURCE – Warner-Lambert.

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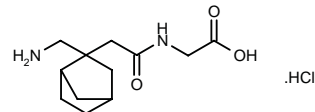
255700

2-[2-(Aminomethyl)bicyclo[2.2.1]hept-2-yl]acetic acid methyl ester hydrochloride



C11-H19-N-O2.HCl; Mol wt: 233.74

ACTION – Anticonvulsant and neuronal injury inhibitor, also claimed for the treatment of depression and anxiety; it is expected to possess activity similar to gabapentin and appears to act as a GABA agonist or GABA mimetic. Other specifically claimed bridged cyclic amino acids include the following:



256821: C12-H20-N2-O3.HCl

SOURCE – Warner-Lambert.

REFERENCES

1. Horwell, D.C. et al. (Warner-Lambert Co.) *Novel bridged cyclic amino acids as pharmaceutical agents*. WO 9733859.

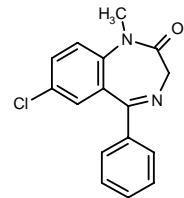
DIAZEPAM

New formulation

Rec INN; BAN; JAN; USAN

091323

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one



C16-H13-Cl-N2-O; Mol wt: 284.74

ACTION – New gel formulation of the benzodiazepine diazepam with anticonvulsant activity.

INDICATION – Management of selected refractory patients with epilepsy on stable regimens of antiepileptic drugs (AEDs) who require intermittent use of diazepam to control bouts of increased seizure activity (clusters).

PRESENTATION – Gel in a prefilled unit-dose rectal delivery system in dosage strengths of 2.5, 5.0 and 10.0 mg (pediatric, 4.4-cm rectal tip size), and 10.0, 15.0 and 20.0 mg (adult, 6.0-cm rectal tip size).

PROPRIETARY NAME – *Diastat* (US).

SOURCES – Athena Neurosciences; Elan.

RECENT REFERENCES

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2. Elan acquires rights to diazepam gel formulation. Prous Science Daily Essentials June 7, 1996.

3. Elan Corporation, plc acquires rights to Athena Neurosciences' Diastat development program. Athena Neurosciences Inc. Press Release 1996, June 4.

4. FDA approves Elan's Diastat, first approved at-home treatment specifically for breakthrough seizure clusters. Elan Corporation plc Press Release 1997, July 31.

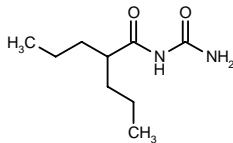
5. First approval for Elan's Diastat. Prous Science Daily Essentials August 8, 1997.

6. New formulation of diazepam launched in U.S. Prous Science Daily Essentials October 21, 1997.

VPU

256865

N-(2-Propylpentanoyl)urea



C9-H18-N2-O2; Mol wt: 186.25

ACTION – Anticonvulsant, a valproic acid analog demonstrated to provide protection in the maximal electroshock (MES) model (ED₅₀ = 66 mg/kg i.p., 413 mg/kg p.o., 0.5 h postdose) and the pentylenetetrazol (PTZ) test in mice (ED₅₀ = 57 mg/kg i.p.), to be weakly active against bicuculline-induced seizures in mice (ED₅₀ = 331 mg/kg i.p.) and inactive against strychnine-induced seizures in mice (ED₅₀ > 400 mg/kg i.p.). Based on its acute toxicity (LD₅₀ = 1553 mg/kg i.p.) and neurological toxicity (TD₅₀ = 625 mg/kg i.p. in the rotarod test in mice), the compound appears to possess a superior safety margin compared to valproic acid (TD₅₀/ED₅₀ MES = 9.5 vs. 1.1; TD₅₀/ED₅₀ PTZ = 11.0 vs. 2.8; LD₅₀/ED₅₀ MES = 23.5 vs. 3.5; LD₅₀/ED₅₀ PTZ = 27.2 vs. 8.8).

SOURCE – Chulalongkorn Univ., Bangkok (TH).

REFERENCES

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THERAPY OF IMMUNOLOGIC
NEUROMUSCULAR DISORDERS

IR-208

229898

T-cell receptor (TCR) Vβ6 CDR2 region peptide vaccine consisting of TCRVβ6.5 peptide 39-58

H-Leu-Gly-Gln-Gly-Pro-Glu-Phe-Leu-Thr-Tyr-Phe-Gln-Asn-Glu-Ala-Gln-Leu-Glu-Lys-Ser-OH

C104-H155-N25-O34; Mol wt: 2299.52

ACTION – Therapeutic T-cell receptor vaccine for the treatment of multiple sclerosis (MS) expected to act by inactivating or eliminating disease-causing T-cells. It has been shown to induce a positive immune response in MS patients at doses of 100 or 300 μg i.m., as well as a reduction in a subset of activated CD4+ T-cells in the cerebrospinal fluid (CSF) and a marked reduction in Vβ6 mRNA levels in T-cells. Currently in phase II trials.

SOURCE – Immune Response Corp.

REFERENCES

1. Brostoff, S. T cell receptor peptide vaccination as immunotherapy for multiple sclerosis. IBC Conf Adv Underst Treat Multiple Sclerosis (June 17-18, San Francisco) 1996.

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5. Immune Response's TCR vaccine evaluated in MS patients. Prous Science Daily Essentials August 28, 1997.

6. In development: Biotechnology medicines. Pharmaceutical Research and Manufacturers of America 1995, March.

7. TCR peptide vaccine induces immune response in MS. Prous Science Daily Essentials June 30, 1997.

8. The Immune Response Corp. Annual Report 1995.

9. The Immune Response Corp. Shareholder Information 1995, March 15.

TREATMENT OF NAUSEA
AND VOMITING

DOLASETRON MESILATE

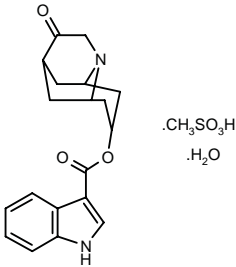
Rec INN; BANM; USAN

151754

1H-Indole-3-carboxylic acid (2α,6α,8α,9αβ)-2,6-methano-3-oxooctahydro-2H-quinolizin-8-yl ester monomethanesulfonate monohydrate

MDL-73147EF+

MDL-74156 [as (+)-isomer]



C19-H20-N2-O3.C-H4-O3-S.H2-O; Mol wt: 438.49

ACTION – Antiemetic agent, a 5-HT₃ receptor antagonist.

INDICATION – Treatment of postoperative nausea and vomiting and nausea and vomiting caused by chemotherapy.

PRESENTATION – *Postoperative*: tablets, 50 mg equiv. to 37 mg dolasetron; ampules, 12.5 mg equiv. to 9.3 mg dolasetron. *Chemotherapy*: tablets, 200 mg equiv. to 148 mg dolasetron; ampules, 100 mg equiv. to 74 mg dolasetron.

PROPRIETARY NAME – Anemet (DE).

SOURCE – Hoechst Marion Roussel.

RECENT REFERENCES

1. Audhuy, B. et al. *Pooled dose response analysis across eight clinical trials assessing the acute antiemetic efficacy of IV dolasetron mesylate (DM) after emetogenic chemotherapy (CT)*. 6th Int Cong Anti-Cancer Treat (Feb 6-9, Paris) 1996, Abst 194.
2. Audhuy, B. et al. *A double-blind, randomised comparison of the anti-emetic efficacy of two intravenous doses of dolasetron mesilate and granisetron in patients receiving high dose cisplatin chemotherapy.* Eur J Cancer 1996, 32A(5): 807.
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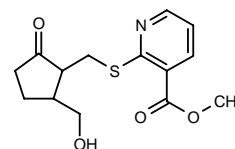
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*Annu Drug Data Rep 1989, 11(8): 621, 1993, 15 (Indices).

COGNITION-ENHANCING DRUGS

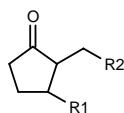
254937

2-[2-(Hydroxymethyl)-5-oxocyclopent-1-ylmethylsulfanyl]-pyridine-3-carboxylic acid methyl ester



C14-H17-N-O4-S; Mol wt: 295.35

ACTION – Neuronal differentiation promoter, as demonstrated in PC12 cell cultures where it exhibited a minimum effective dose (MED) of 0.20 µg/ml. Other compounds from this series of 2,3-disubstituted cyclopentanone derivatives include the following:



Compound	R1	R2	Formula
256824	CH ₂ OAc	SCH ₂ CH(OH)CH ₂ OH	C ₁₂ H ₂₀ O ₅ S
256825	CH ₂ OAc	SCH ₂ CH(CO ₂ H)NHAc	C ₁₄ H ₂₁ NO ₆ S
256826	CH ₂ OH	SCH ₂ CH(CO ₂ H)NHAc	C ₁₂ H ₁₉ NO ₅ S
256827	CH ₂ OAc	SCH ₂ CH ₂ NHAc	C ₁₃ H ₂₁ NO ₄ S
256828	CH ₂ OAc	SCH ₂ CH ₂ OH	C ₁₁ H ₁₈ O ₄ S
256829	CO ₂ H	SCH ₂ CH(CO ₂ Me)NHAc	C ₁₃ H ₁₉ NO ₆ S
256830	CO ₂ H	allyl-OCOCH(NHAc)CH ₂ S	C ₁₅ H ₂₁ NO ₆ S
256831	CO ₂ H	SCH ₂ CH(CO ₂ H)NHAc	C ₁₂ H ₁₇ NO ₆ S
256832	CO ₂ Me	SCH ₂ CH(CO ₂ H)NHAc	C ₁₃ H ₁₉ NO ₆ S
256833	CO ₂ Me	SCH ₂ CH ₂ NHAc	C ₁₂ H ₁₉ NO ₄ S
256834	CO ₂ H	SCH ₂ CH ₂ NHAc	C ₁₁ H ₁₇ NO ₄ S
256835	CH ₂ OH	OCH ₂ CH(OH)CH ₂ OH	C ₁₀ H ₁₈ O ₅

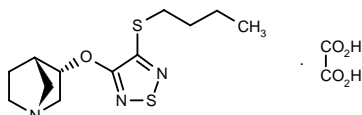
SOURCE – Nippon Kayaku.

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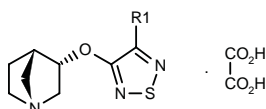
256167

endo-3-[4-(Butylsulfanyl)-1,2,5-thiadiazol-3-yloxy]-1-azabicyclo[2.2.1]heptane oxalate



C12-H19-N3-O-S2.C2-H2-O4; Mol wt: 375.46

ACTION – Cognition-enhancing agent with potent affinity for muscarinic cholinergic receptors, as demonstrated by its ability to inhibit [³H]-oxotremorine and [³H]-pirenzepine binding in rat cortex preparations (IC₅₀ = 1.6 and 0.14 nM, respectively). Also potentially useful for the treatment of severe painful conditions, glaucoma, schizophrenia, depression, anxiety and sleep disorders. Other heterocyclic compounds include the following:



Compound	R1	Formula
256952	SPr	C ₁₁ H ₁₇ N ₃ OS ₂ C ₂ H ₂ O ₄
256953	3-furyl-ethynylene-CH ₂ O	C ₁₅ H ₁₅ N ₃ O ₃ S ₂ C ₂ H ₂ O ₄
256954	3-thienyl-ethynylene-CH ₂ O	C ₁₅ H ₁₅ N ₃ O ₃ S ₂ C ₂ H ₂ O ₄

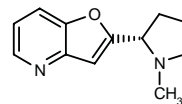
SOURCE – Novo Nordisk.

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256883

2-[1-Methylpyrrolidin-2(S)-yl]furo[3,2-b]pyridine



C12-H14-N2-O; Mol wt: 202.26

ACTION – Potent and selective neuronal nicotinic acetylcholine receptor (nAChR) modulator with high functional selectivity for the neuronal $\alpha_4\beta_2$ nAChR subtype; it had high affinity for the nAChR labeled by [³H]-cytisine (K_i = 2.73 ± 0.45 nM in rat brain preparations). The compound was evaluated for functional activity in IMR-32 cells expressing the human $\alpha_3\beta_x$ nAChR subtype, K177 cells expressing the human $\alpha_4\beta_2$ nAChR subtype and TE671 cells expressing the human α_1 neuromuscular nAChR subtype, showing agonist activity at $\alpha_4\beta_2$ receptors (EC₅₀ 3.2 ± 2.5 μ M; intrinsic activity relative to (S)-nicotine = 81 ± 15%), and very weak activity at the $\alpha_3\beta_x$ subtype (EC₅₀ > 1000 μ M; intrinsic activity = 10.6 ± 4.5%) related to undesirable cardiovascular and gastrointestinal side effects associated with nicotine, and at the α_1 neuromuscular subtype (EC₅₀ > 100 μ M; intrinsic activity = 18.9%). Potentially useful for the treatment of cognitive disorders without the undesirable side effects associated with other less specific neuronal nAChR ligands.

SOURCE – Abbott.

REFERENCES

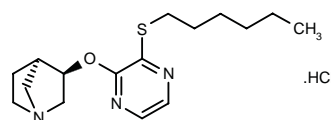
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WAY-132983

257396

(3*R*,4*R*)-3-[3-(Hexylsulfanyl)pyrazin-2-yloxy]-1-azabicyclo[2.2.1]heptane hydrochloride



C16-H25-N3-O-S.HCl; Mol wt: 343.91

ACTION – Agent for the treatment of cognition disorders such as Alzheimer's disease with muscarinic receptor-agonist activity. Compound displaced [³H]-QNB binding in CHO cells expressing muscarinic receptor subtypes with 5-20 times the affinity of xanomeline; it potently stimulated phosphatidylinositol hydrolysis in cell lines expressing m1, m3 and m5 receptors (EC₅₀ = 1.1, 3.7 and 2.7 nM, respectively) and inhibited forskolin-enhanced cAMP production in cell lines expressing m2 and m4 receptors. In rats, the compound significantly reduced scopolamine- and AF64A-induced cognitive impairment at doses of 0.3 mg/kg i.p. and 0.03 mg/kg/day by osmotic minipump, respectively, being more potent than xanomeline. In aged monkeys (0.003-0.10 mg/kg p.o.), it significantly improved delayed matching-to-sample performance, with mnemonic effects seen for up to 24 h following administration.

SOURCE – American Home Products.

REFERENCES

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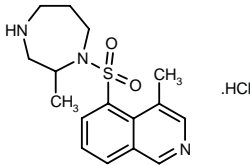
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TREATMENT OF
CEREBROVASCULAR DISEASES

254945

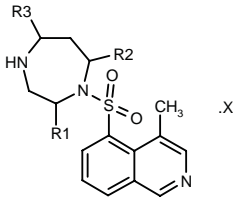
2-Methyl-1-(4-methylisoquinolin-5-ylsulfonyl)perhydro-1,4-diazepine hydrochloride

(4-Methylisoquinolin-5-yl)(2-methylperhydro-1,4-diazepin-1-yl)sulfone hydrochloride



C16-H21-N3-O2-S.HCl; Mol wt: 355.88

ACTION – Cerebral vasodilating and neuroprotective agent with potential in the prevention and treatment of cerebrovascular disorders such as cerebral vasospasm following subarachnoid hemorrhage. Compound was more potent than fasudil hydrochloride in relaxing rat aorta strips contracted with calcium ionophore A23187 (IC₅₀ = 0.74 and 5.2 μM, respectively). *In vivo*, it was also found to exhibit superior vasodilating and neuroprotective properties compared to fasudil hydrochloride in several animal models. A representative compound from a series of isoquinoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	X	Formula
256590	(S)-Me	H	H	HCl	C ₁₆ H ₂₁ N ₃ O ₂ S.HCl
256591	H	H	Me	2HCl	C ₁₆ H ₂₁ N ₃ O ₂ S.2HCl
256592	(R)-Me	H	H	HCl	C ₁₆ H ₂₁ N ₃ O ₂ S.HCl
256593	H	Me	H	2HCl	C ₁₆ H ₂₁ N ₃ O ₂ S.2HCl
256594	H	H	H	2HCl	C ₁₅ H ₁₉ N ₃ O ₂ S.2HCl

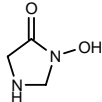
SOURCE – Nippon Shinyaku.

REFERENCES

1. Matsuura, A. and Matsuzaki, T. (Nippon Shinyaku Co., Ltd.) *Isoquinoline derivs. and drugs*. WO 9728130.

255397

3-Hydroxyimidazolidin-4-one



C3-H6-N2-O2; Mol wt: 102.09

ACTION – A potent partial agonist of the glycine receptor site on the NMDA receptor complex, as demonstrated in binding studies by an IC₅₀ value of 6.8 μM for [³H]-glycine binding in rat brain membranes and an EC₅₀ of 4.3 μM for [³H]-MK-801 binding in rat brain membranes, and a maximum stimulating effect on the latter of 46%. Potentially useful for the treatment of disorders such as neurodegenerative and neurological disorders, schizophrenia and anxiodepressive conditions.

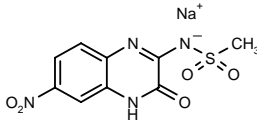
SOURCE – ADIR.

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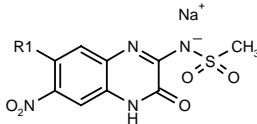
255667

N-(6-Nitro-3-oxo-3,4-dihydroquinoxalin-2-yl)methanesulfonamide sodium salt



C9-H7-N4-Na-O5-S; Mol wt: 306.23

ACTION – Glutamate receptor antagonist with potential in the treatment or prevention of anxiety, depression, schizophrenia, epilepsy, cognition disorders, stroke, cerebral ischemia, head trauma, spinal cord trauma, cardiac arrest, hypoglycemia, anoxia, convulsions, brain edema, Alzheimer's disease, Huntington's chorea, Parkinson's disease and opiate tolerance and withdrawal. A representative compound from a series of specifically claimed quinoxaline derivatives, wherein the following are also included:



Compound	R1	Formula
256554	1-imidazolyl	C ₁₂ H ₉ N ₆ NaO ₅ S
256555	4-oxo-1,4-dihydro-1-Pyr	C ₁₄ H ₁₀ N ₅ NaO ₆ S

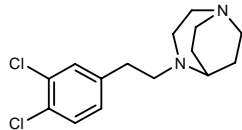
SOURCE – Fujisawa.

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1. Nakai, K. et al. (Fujisawa Pharm. Co., Ltd.) *Quinoxaline derivs. as glutamate receptor antagonists*. WO 9732858.

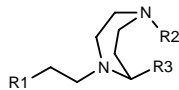
255794

4-[2-(3,4-Dichlorophenyl)ethyl]-1,4-diazabicyclo[3.2.2]-nonane



C15-H20-Cl2-N2; Mol wt: 299.24

ACTION – Agent for the treatment of cerebral ischemia, neurodegenerative disorders and neurotoxic injury, psychosis and convulsions, a σ -receptor ligand (K_i = 125 nM against [³H]-(+)-pentazocine binding in guinea pig brain membranes). Other specifically claimed compounds from this series of aralkyl bridged diazabicycloalkane derivatives include the following:



Compound	R1	R2,R3	Formula
255995	3-benzothieryl	-(CH2)2-	C ₁₇ H ₂₂ N ₂ S
255996	2-Naph	-(CH2)2-	C ₁₉ H ₂₄ N ₂
255997	3,4-(Cl)2-Ph	-(CH2)3-	C ₁₈ H ₂₂ Cl ₂ N ₂
255998	3-benzothieryl	-(CH2)4-	C ₁₉ H ₂₆ N ₂ S
255999	2-Naph	-(CH2)5-	C ₂₂ H ₃₀ N ₂

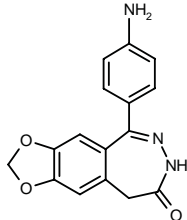
SOURCE – Dept. Health Human Services (US).

REFERENCES

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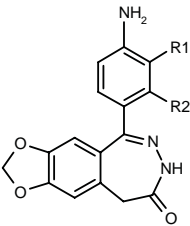
256154

5-(4-Aminophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h]-[2,3]benzodiazepin-8-one



C16-H13-N3-O3; Mol wt: 295.30

ACTION – Neuroprotective and cerebral antiischemic agent and anticonvulsant, an AMPA receptor antagonist (IC_{50} = 3 μ M for inhibition of AMPA-induced current in neuronal AMPA receptor-expressing oocytes). Compound exhibited significant anticonvulsant activity in the maximal electroshock seizure test in mice (ED_{50} = 2.4 mg/kg i.v.). Other compounds from this series of substituted 2,3-benzodiazepin-4-ones include the following:



Compound	R1	R2	Formula
257346	Me	H	C ₁₇ H ₁₅ N ₃ O ₃
257347	H	Cl	C ₁₆ H ₁₂ ClN ₃ O ₃

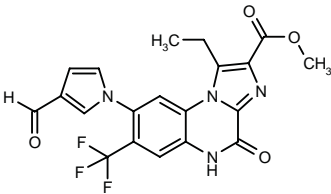
SOURCES – ACEA; CoCensys.

REFERENCES

1. Xiai, H. et al. (CoCensys, Inc.; ACEA Pharm., Inc.) *Substd. 2,3-benzodiazepin-4-ones and the use thereof*. WO 9734878.

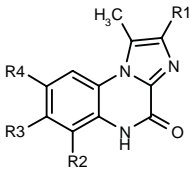
256165

1-Ethyl-8-(3-formylpyrrol-1-yl)-4-oxo-7-(trifluoromethyl)-4,5-dihydroimidazo[1,2-a]quinoxaline-2-carboxylic acid methyl ester



C20-H15-F3-N4-O4; Mol wt: 432.36

ACTION – Agent for the treatment of neurodegenerative diseases, as well as epilepsy, anxiety and depression, an NMDA receptor antagonist. Within this series of heterocyclic substituted imidazoloquinoxalinones, the following are also included:



Compound	R1	R2	R3	R4	Formula
257098	CO ₂ Et	-CH=CHCH=CH-		3-CHO-1-pyrrolyl	C ₂₃ H ₁₈ N ₄ O ₄
257099	CO ₂ Et	-CH=CHCH=CH-		3-(PhNHCONH-CH ₂)-1-pyrrolyl	C ₃₀ H ₂₆ N ₆ O ₄
257100	CH ₂ CO ₂ Et	H	NO ₂	4-Me-1-imidazolyl	C ₁₉ H ₁₈ N ₆ O ₅
257101	CH ₂ CO ₂ Me	H	CF ₃	4-Ph-1-imidazolyl	C ₂₄ H ₁₈ F ₃ N ₅ O ₃
257102	CH ₂ CO ₂ H	H	CF ₃	4-Ph-1-imidazolyl	C ₂₃ H ₁₆ F ₃ N ₅ O ₃

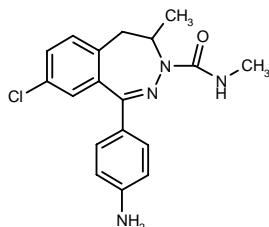
SOURCE – BASF.

REFERENCES

1. Treiber, H.-J. et al. (BASF AG) *Novel heterocyclically substd. imidazoloquinoxalinones, their preparation and their use*. WO 9734896.

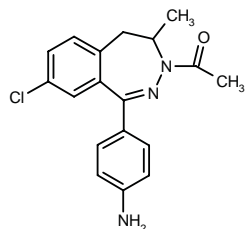
256351

1-(4-Aminophenyl)-8-chloro-*N*,4-dimethyl-4,5-dihydro-3*H*-2,3-benzodiazepine-3-carboxamide



C18-H19-Cl-N4-O; Mol wt: 342.83

ACTION – Agent for the treatment of epilepsy and acute or chronic neurodegenerative disorders that acts by antagonizing AMPA receptors, as demonstrated by inhibition of kainate-induced retinal spreading depression (IC_{50} = 4.6 μ M). Another specifically claimed 2,3-benzodiazepine derivative is:



257490: C18-H18-Cl-N3-O

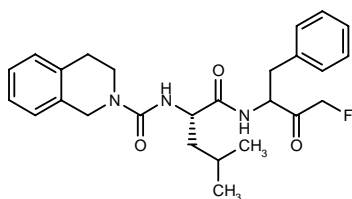
SOURCE – Egis.

REFERENCES

1. Ling, I. et al. (Egis Gyosgysszergyar RT) *Substd. 2,3-benzodiazepine derivs., process and intermediates for their preparation and pharmaceutical compsns. comprising them as well as their use.* EP 802195, FR 2747121, GB 2311779.

257084

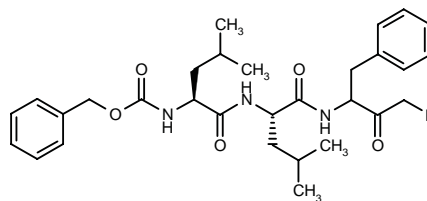
1,2,3,4-Tetrahydroisoquinolin-2-ylcarbonyl-L-leucine (1-benzyl-3-fluoro-2-oxopropyl)amide



C26-H32-F-N3-O3; Mol wt: 453.56

White solid.

ACTION – Neuroprotective agent, a potent inhibitor of calpain I, as demonstrated in an enzyme assay and by inhibition of the calpain I-mediated formation of spectrin breakdown products in MOLT-4 cells (IC_{50} = 0.2 μ M), with moderate selectivity over cathepsin B and L. The most potent dipeptide fluoromethyl ketone calpain I inhibitor reported to date, with potential in the treatment of stroke. Another fluoromethyl ketone is:



257085: C30-H40-F-N3-O5

SOURCE – Cephalon.

REFERENCES

1. Chatterjee, S. et al. *Potent fluoromethyl ketone inhibitors of recombinant human calpain I.* Bioorg Med Chem Lett 1996, 6(11): 1237.
2. Chatterjee, S. et al. *Synthesis and biological activity of a series of potent fluoromethyl ketone inhibitors of recombinant human calpain I.* J Med Chem 1997, 40(23): 3820.

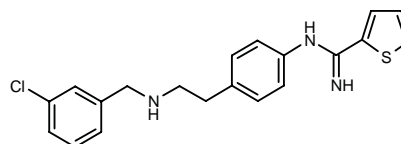
AR-R-17477

225416

N-[4-[2-(3-Chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine

ARL-17477

FPL-17477



C20-H20-Cl-N3-S; Mol wt: 369.91

ACTION – Neuroprotective agent, a potent and selective neuronal nitric oxide synthase (nNOS) inhibitor. In a model of transient focal cerebral ischemia in rats subjected to middle cerebral artery (MCA) occlusion followed by reperfusion, it reduced infarct volume by over 50% at a dose (1 mg/kg i.v. at reperfusion and 0.3 mg/kg i.v. at 24 and 48 h of reperfusion) having no effect on cerebral blood flow (rCBF); at 1-10 mg/kg i.v. it inhibited brain NOS by 35-90%, without increasing mean arterial blood pressure.

SOURCES – Astra Arcus.

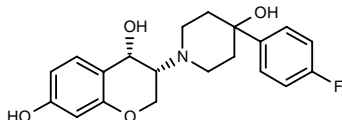
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1. Gentile, R.J. et al. (Fisons Corp.; Fisons plc) *Amidine derivs. with nitric oxide synthetase activities.* EP 713483, JP 97501918, WO 9505363.
2. Harukuni, I. et al. *Effect of ARL 17477, a selective neuronal NOS inhibitor, in rats subjected to permanent focal ischemia.* Stroke 1997, 28(1): Abst 126.
3. Macdonald, J.E. et al. *N-Phenylthiophenecarboximidamides: Potent and selective inhibitors of neuronal NOS.* 5th Chem Cong North Amer (Nov 11-15, Cancun) 1997, Abst 02-549.
4. Zhang, Z.G. et al. *Selective neuronal NOS inhibitor decreases infarct volume after transient focal cerebral ischemia in rats.* J Cerebr Blood Flow Metab 1995, 15(Suppl. 1): Abst XVII-4.
5. Zhang, Z.G. et al. *ARL 17477, a potent and selective neuronal NOS inhibitor decreases infarct volume after transient middle cerebral artery occlusion in rats.* J Cerebr Blood Flow Metab 1996, 16(4): 599.

CP-283097

257397

(+)-(3*R*,4*S*)-3-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]-3,4-dihydro-2*H*-1-benzopyran-4,7-diol



C20-H22-F-N-O4; Mol wt: 359.40

ACTION – Neuroprotective agent, a conformationally restricted analog of CP-101606 that acts as an NMDA receptor antagonist with selectivity for the NR2B subtype. The compound selectively inhibited [³H]-CP-101606 binding to rat forebrain membranes with a K_i of 12 ± 2 nM, with no effect at glutamate or glycine binding sites; it potently inhibited glutamate-induced neuronal loss in rat primary hippocampal neuronal cultures ($IC_{50} = 8 \pm 5$ nM), whereas it was much less effective against glutamate toxicity in rat cerebellar granule neuron cultures. It inhibited the accumulation of Fos protein (MED = 3.2 mg/kg i.v.) in rats following cortical injury, as well as the expression of *c-fos* mRNA in mice following a subconvulsant dose of NMDA ($ED_{50} = 4$ mg/kg i.p.). It also inhibited haloperidol-induced catalepsy in rats ($ED_{50} = 0.3$ mg/kg s.c., 1.2 mg/kg p.o.).

SOURCE – Pfizer.

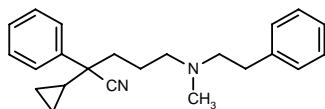
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- Butler, T.W. et al. CP-283,097, a conformationally restricted analog of CP-101,606: Structure activity relations. Soc Neurosci Abstr 1997, 23(Part 1): Abstr 367.2.
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E-5608

257113

(-)-2-Cyclopropyl-5-[*N*-methyl-*N*-(2-phenylethyl)amino]-2-phenylpentanenitrile



C23-H28-N2; Mol wt: 332.49

ACTION – Neuroprotective agent with calcium-antagonist activity ($pA_2 = 6.98$ in rat aorta). The compound displayed better activity in the nitrogen-induced anoxia model in mice ($ED_{50} = 12$ mg/kg) than in the barium chloride-induced mortality test in mice ($ED_{50} = 60$ mg/kg), suggesting greater central activity than peripheral activity. In rats with permanent focal cerebral ischemia, it demonstrated activity comparable to that of emopamil at a dose of 40 mg/kg i.p. given before and after occlusion.

SOURCE – Esteve.

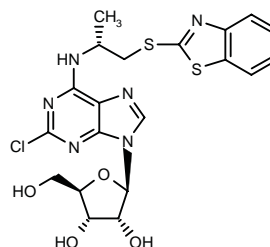
REFERENCES

- Corbera-Arjona, J. and Frigola-Constans, J. (Lab. Dr. Esteve) *Cyclopropylacetone nitrile derivs., preparation thereof and use thereof as drugs*. EP 699182, FR 2717473, JP 96510476, WO 9525087.
- Fisas, M.A. et al. *Pharmacological profile of new series of calcium-antagonists as neuroprotectants*. Meth Find Exp Clin Pharmacol 1997, 19(Suppl. A): Abstr PA-25.

NNC-21-0136

257399

2-Chloro-*N*⁶-[2-(2-benzothiazolylsulfanyl)-1(*R*)-methyl-ethyl]adenosine



C20-H21-Cl-N6-O4-S2; Mol wt: 509.00

ACTION – Prototype neuroprotectant for the acute treatment of stroke, a potent adenosine A_1 receptor agonist ($K_i = 10$ nM in rat brain preparations) with selectivity over A_{2A} receptors ($K_i = 660$ nM); it exhibited full agonist activity in a functional assay and no significant affinity for human A_3 receptors. The compound produced a relatively weak inotropic effect on spontaneously beating isolated guinea pig atria ($IC_{50} = 6200$ nM); in mice, it dose-dependently reduced locomotor activity and showed anticonvulsant and hypothermic properties, but these effects were significantly reduced compared to reference A_1 agonists.

SOURCE – Novo Nordisk.

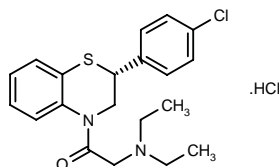
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- Knutsen, L.J.S. et al. *Novel neuroprotectant adenosine A_1 receptor agonists: Structure activity relationships (SAR) of 2-chloro-*N*-[*R*-(2-benzothiazolyl)thio-2-propyl]adenosine (NNC 21-0136)*. Soc Neurosci Abstr 1997, 23(Part 2): Abstr 745.14.
- Sheardown, M.J. et al. *Pharmacological profile of the stroke drug candidate, 2-chloro-*N*-[*R*-(2-benzothiazolyl)thio-2-propyl]adenosine (NNC 21-0136) a novel adenosine A_1 receptor agonist*. Soc Neurosci Abstr 1997, 23(Part 2): Abstr 745.15.
- Spedding, M. and Williams, M. *Developments in purine and pyrimidine receptor-based therapeutics*. Drug Develop Res 1996, 39(3-4): 436.

T-477**234446**

(+)-(R)-2-(4-Chlorophenyl)-4-[2-(diethylamino)acetyl]-2,3-dihydro-4H-1,4-benzothiazine hydrochloride

477



C20-H23-Cl-N2-O-S.HCl; Mol wt: 411.39

ACTION – Neuroprotective agent, a neuronal Ca^{2+} and Na^{+} channel blocker structurally similar to diltiazem. When given before and after middle cerebral artery (MCA) occlusion (total dose of 25 mg/kg i.v.) or only after occlusion (total dose of 7.5 mg/kg i.v.), it was able to decrease the volume of ischemic damage in rats by 19-23%, without altering blood pressure, heart rate, PCO_2 , PO_2 or blood pH.

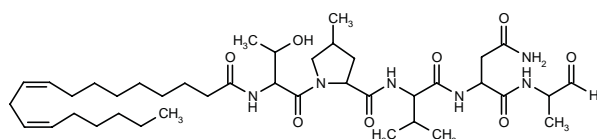
SOURCE – Tanabe Seiyaku.

REFERENCES

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3. Ishii, T. et al. *T-477, a novel neuronal Ca^{2+} and Na^{+} channel blocker, reduces infarct volume following middle cerebral artery occlusion in rats*. Jpn J Pharmacol 1996, 71(Suppl. 1): Abst P-468.
4. Kobayashi, T. et al. *Effect of a new potential neuroprotective agent, T-477, on cloned cardiac- and brain-type Ca^{2+} channels expressed in *Xenopus* oocytes*. Jpn J Pharmacol 1996, 71(Suppl. 1): Abst P-467.
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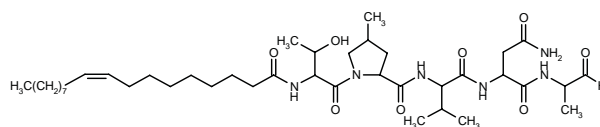
WF-10225A**255516**

9(Z),12(Z)-Octadecadienoyl-D,L-threonyl-D,L-(4-methyl)-prolyl-D,L-valyl-D,L-asparaginyl-D,L-alaninal



C40-H68-N6-O8; Mol wt: 761.01

ACTION – Calpain I inhibitor (IC_{50} = 0.78 $\mu\text{g/ml}$ against pig enzyme) with much lower activity against cathepsin B (IC_{50} = 50 $\mu\text{g/ml}$ against human enzyme), isolated from the culture of a strain of the genus *Spirosphaera* such as *Spirosphaera floriformis* 10225 (FERM P-15378). Potentially useful for the treatment or prevention of ischemic disorders such as stroke, myocardial infarction and renal failure. Another related compound is:



WF-10225B [257278]: C40-H70-N6-O8

SOURCE – Fujisawa.

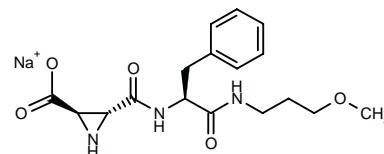
REFERENCES

1. Fujie, K. et al. (Fujisawa Pharm. Co., Ltd.) *Methylproline cpds., method for their production and their use*. JP 97221497.

MISCELLANEOUS NEUROLOGIC DRUGS

255509

N-[3(R)-Carboxyaziridin-2(R)-ylcarbonyl]-L-phenylalanine 3-methoxypropylamide sodium salt



C17-H22-N3-Na-O5; Mol wt: 371.37

ACTION – Agent for the treatment of muscular dystrophy, osteoporosis, malignant hypercalcemia, Paget's disease and myocardial infarction, an inhibitor of cathepsin L (IC_{50} = 1.8 ng/ml using human recombinant enzyme).

SOURCE – Takeda.

REFERENCES

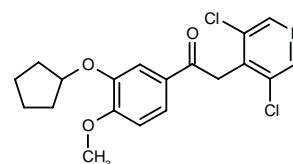
1. Tsubotani, S. et al. (Takeda Chem. Ind., Ltd.) *Aziridine dicarboxylic acid derivs., method for their production and their use*. JP 97221470.

RESPIRATORY DRUGS

ASTHMA THERAPY

255798

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(3,5-dichloro-4-pyridyl)ethanone

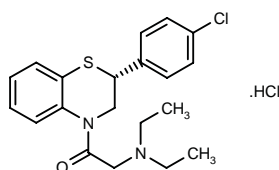


C19-H19-Cl2-N-O3; Mol wt: 380.27

T-477**234446**

(+)-(R)-2-(4-Chlorophenyl)-4-[2-(diethylamino)acetyl]-2,3-dihydro-4H-1,4-benzothiazine hydrochloride

477



C20-H23-Cl-N2-O-S.HCl; Mol wt: 411.39

ACTION – Neuroprotective agent, a neuronal Ca^{2+} and Na^{+} channel blocker structurally similar to diltiazem. When given before and after middle cerebral artery (MCA) occlusion (total dose of 25 mg/kg i.v.) or only after occlusion (total dose of 7.5 mg/kg i.v.), it was able to decrease the volume of ischemic damage in rats by 19-23%, without altering blood pressure, heart rate, PCO_2 , PO_2 or blood pH.

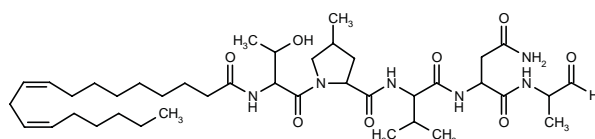
SOURCE – Tanabe Seiyaku.

REFERENCES

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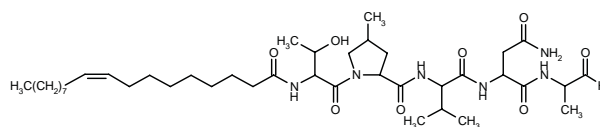
WF-10225A**255516**

9(Z),12(Z)-Octadecadienoyl-D,L-threonyl-D,L-(4-methyl)-prolyl-D,L-valyl-D,L-asparaginyl-D,L-alaninal



C40-H68-N6-O8; Mol wt: 761.01

ACTION – Calpain I inhibitor (IC_{50} = 0.78 $\mu\text{g/ml}$ against pig enzyme) with much lower activity against cathepsin B (IC_{50} = 50 $\mu\text{g/ml}$ against human enzyme), isolated from the culture of a strain of the genus *Spirosphaera* such as *Spirosphaera floriformis* 10225 (FERM P-15378). Potentially useful for the treatment or prevention of ischemic disorders such as stroke, myocardial infarction and renal failure. Another related compound is:

**WF-10225B [257278]:** C40-H70-N6-O8

SOURCE – Fujisawa.

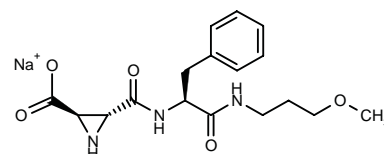
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MISCELLANEOUS NEUROLOGIC DRUGS

255509

N-[3(R)-Carboxyaziridin-2(R)-ylcarbonyl]-L-phenylalanine 3-methoxypropylamide sodium salt



C17-H22-N3-Na-O5; Mol wt: 371.37

ACTION – Agent for the treatment of muscular dystrophy, osteoporosis, malignant hypercalcemia, Paget's disease and myocardial infarction, an inhibitor of cathepsin L (IC_{50} = 1.8 ng/ml using human recombinant enzyme).

SOURCE – Takeda.

REFERENCES

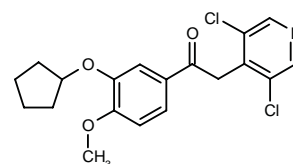
1. Tsubotani, S. et al. (Takeda Chem. Ind., Ltd.) *Aziridine dicarboxylic acid derivs., method for their production and their use*. JP 97221470.

RESPIRATORY DRUGS

ASTHMA THERAPY

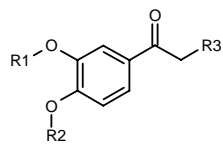
255798

1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-(3,5-dichloro-4-pyridyl)ethanone



C19-H19-Cl2-N-O3; Mol wt: 380.27

ACTION – An inhibitor of the production of tumor necrosis factor (TNF) and of type IV cAMP phosphodiesterase (PDE IV), potentially useful in particular for the treatment of asthma or joint inflammation. Other specifically claimed substituted phenyl compounds include the following:



Compound	R1	R2	R3	Formula
256003	cyclopentyl	Me	2,6-(Cl)2-Ph	C ₂₀ H ₂₀ Cl ₂ O ₃
256004	cyclopentyl	Me	3,5-(Cl)2-1-oxido-4-Pyr-	C ₁₉ H ₁₉ Cl ₂ NO ₄
256005	exo-bicyclo-[2.2.1]hept-2-yl	Me	3,5-(Cl)2-4-Pyr	C ₂₁ H ₂₁ Cl ₂ NO ₃
256006	exo-bicyclo-[2.2.1]hept-2-yl	CHF2	3,5-(Cl)2-4-Pyr	C ₂₁ H ₁₉ Cl ₂ F ₂ NO ₃
256007	exo-bicyclo-[2.2.1]hept-5-en-2-yl	Me	3,5-(Cl)2-4-Pyr	C ₂₁ H ₁₉ Cl ₂ NO ₃
256008	exo-bicyclo-[2.2.1]hept-2-yl	CHF2	3,5-(Cl)2-1-oxido-4-Pyr-	C ₂₁ H ₁₉ Cl ₂ F ₂ NO ₄

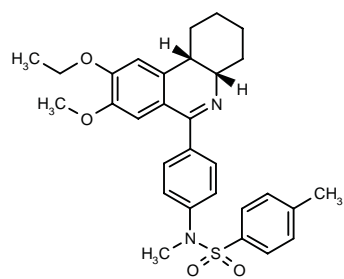
SOURCE – Rhône-Poulenc Rorer.

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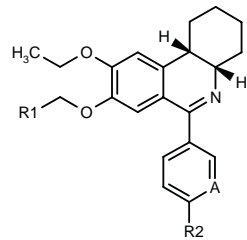
256204

(±)-*cis-N*-[4-[9-Ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydrophenanthridin-6-yl)phenyl]-*N*,4-dimethylbenzenesulfonamide



C30-H34-N2-O4-S; Mol wt: 518.67

ACTION – Bronchodilating agent, a potent inhibitor of phosphodiesterase type IV (–log IC₅₀ = 9.09). Other representative compounds within this series of phenanthridines include the following:



Compound	R1	R2	A	Formula
257493	Me	4-Me-PhSO2NH	CH	C ₃₀ H ₃₄ N ₂ O ₄ S
257494	Me	OAc	CH	C ₂₅ H ₂₉ NO ₄

Compound	R1	R2	A	Formula
257495	H	4-Me-PhSO2NH	CH	C ₂₉ H ₃₂ N ₂ O ₄ S
257496	H	NO2	CH	C ₂₂ H ₂₄ N ₂ O ₄
257497	H	SO2Me	CH	C ₂₃ H ₂₇ NO ₄ S
257499	Me	Cl	N	C ₂₂ H ₂₅ ClN ₂ O ₂
257500	H	NHAc	CH	C ₂₄ H ₂₈ N ₂ O ₃

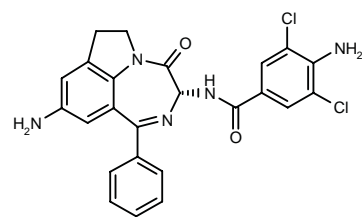
SOURCE – Byk Gulden.

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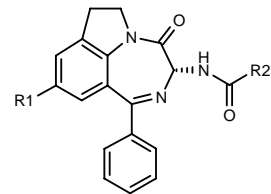
257183

4-Amino-*N*-[9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-3(*R*)-yl]-3,5-dichlorobenzamide



C24-H19-Cl2-N5-O2; Mol wt: 480.35

ACTION – Antiinflammatory, antiallergic, antiasthmatic and bronchodilating agent, a potent and selective phosphodiesterase type IV (PDE IV) inhibitor, proven to be 33-fold more potent than rolipram in U937 cells. *In vivo*, it is reported to significantly inhibit antigen-induced eosinophil infiltration into bronchoalveolar lavage (BAL) in guinea pigs following oral administration (1-30 mg/kg) and to reduce the inflammatory response induced by intra-tracheal instillation of IL-5 in guinea pigs. Other compounds from this series of diazepino-indoles include the following:



Compound	R1	R2	Formula
258106	OH	3-isoquinoliny	C ₂₇ H ₂₀ N ₄ O ₃
258107	NH2	4-NH2-5-Cl-2-MeO-Ph	C ₂₈ H ₂₂ ClN ₅ O ₃
258108	NH2	4-Pyr	C ₂₃ H ₁₉ N ₅ O ₂
258109	NH2	3-(t-BuOCONH)-4-Pyr	C ₂₈ H ₂₈ N ₆ O ₄
258110	NH2	3-isoquinoliny	C ₂₇ H ₂₁ N ₅ O ₂
258111	NH2	3-quinoliny	C ₂₇ H ₂₁ N ₅ O ₂
258112	NH2	4,7-(Me)2-pyrazolo[5,1-c]-[1,2,4]triazin-3-yl	C ₂₅ H ₂₂ N ₆ O ₂
258113	N(Me)2	4-NH2-3,5-(Cl)2-Ph	C ₂₈ H ₂₃ Cl ₂ N ₅ O ₂
258114	NH2	2-benzofuranyl	C ₂₆ H ₂₀ N ₄ O ₃
258115	1-pyrrolidiny	4,7-(Me)2-pyrazolo[5,1-c]-[1,2,4]triazin-3-yl	C ₂₉ H ₂₈ N ₈ O ₂

SOURCE – Jouveinal.

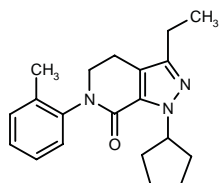
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CP-220629

256686

1-Cyclopentyl-3-ethyl-6-(2-methylphenyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridin-7-one



C20-H25-N3-O; Mol wt: 323.44

ACTION – Antiasthmatic agent, an oral phosphodiesterase type IV (PDE IV) inhibitor proven active in an eosinophil PDE assay ($IC_{50} = 0.44 \mu M$) and in guinea pigs with antigen-induced airways obstruction ($ED_{50} = 2.0 \text{ mg/kg p.o.}$); in atopic monkeys, it produced a significant reduction in eosinophil and IL-1 β responses to antigen challenge (55 and 82%, respectively).

SOURCE – Pfizer.

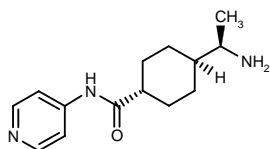
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Y-27632

256939

(+)-*trans*-4-[1(*R*)-Aminoethyl]-*N*-(4-pyridyl)cyclohexane-1-carboxamide



C14-H21-N3-O; Mol wt: 247.34

ACTION – A specific and potent vascular and bronchial smooth muscle relaxant that acts by inhibiting Ca^{2+} sensitization. It inhibited phenylephrine-induced contractions in rabbit aortic strips ($IC_{50} = 0.7 \mu M$), but not potassium chloride-induced contractions ($IC_{50} > 30 \mu M$), and it concentration-dependently inhibited $GTP\gamma S$ -induced contraction in rabbit mesenteric artery strips, with no effect on Ca^{2+} -induced contraction. The compound targets the Rho-associated coiled coil-forming kinase p160ROCK, with good selectivity over protein kinase C, cAMP-dependent protein kinase and myosin light chain kinase ($K_i = 0.14, 26, 25$

and $> 250 \mu M$, respectively), and it inhibited the p160ROCK-mediated formation of stress fibers and focal adhesions in intact cells. In spontaneously, renal and DOCA-salt hypertensive rats, a dose of 30 mg/kg p.o. significantly and persistently reduced blood pressure, whereas in normotensive rats it produced only a slight and transient reduction in blood pressure. Potentially useful in the treatment of hypertension, autoimmune diseases, bronchial asthma and tumor metastasis.

SOURCES – Kyoto Univ., Kyoto (JP); Yoshitomi.

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MONTELUKAST SODIUM

Prop INN; USAN

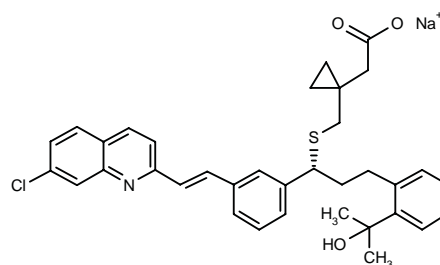
205402

2-[1-[1(*R*)-[3-[2(*E*)-(7-Chloroquinolin-2-yl)vinyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propylsulfanyl-methyl]cyclopropyl]acetic acid sodium salt

L-706631

MK-476⁺

MK-0476



C35-H35-Cl-N-Na-O3-S; Mol wt: 608.17

ACTION – Selective and orally active CysLT₁ receptor antagonist.

INDICATION – Prophylaxis and chronic treatment of asthma, including the prevention of day- and nighttime symptoms, the treatment of aspirin-sensitive asthmatic patients and the prevention of exercise-induced bronchoconstriction, in adults and children aged 6 years and older.

PRESENTATION – Tablets, 10 mg (10.4 mg montelukast sodium equiv. to 10 mg free acid) for adults aged 15 and above; chewable tablets, 5 mg (5.2 mg montelukast sodium equiv. to 5 mg free acid) for children aged 6-14 years.

PROPRIETARY NAME – *Singulair* (FI, MX).

SOURCE – Merck & Co.

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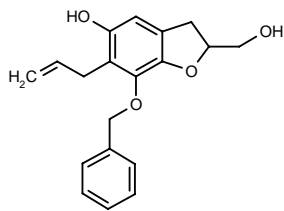
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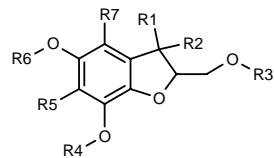
255728

6-Allyl-7-benzyloxy-2-(hydroxymethyl)-2,3-dihydrobenzofuran-5-ol



C19-H20-O4; Mol wt: 312.36

ACTION – Antiallergic and antiinflammatory agent, a 5-lipoxygenase inhibitor with an IC₅₀ of 0.57 μM using rat basophilic leukemia cell preparations. Other representative compounds within this series of benzofuran derivatives include the following:



Compound	R1=R2	R3	R4	R5	R6	R7	Formula
256628	H	H	H	allyl	CH2Ph	H	C ₁₉ H ₂₀ O ₄
256629	H	H	H	H	CH2Ph	allyl	C ₁₉ H ₂₀ O ₄
256630	H	H	CH2Ph	H	H	allyl	C ₁₉ H ₂₀ O ₄
256631	Me	Et	H	allyl	H	H	C ₁₆ H ₂₂ O ₄
256632	Me	Et	H	H	H	allyl	C ₁₆ H ₂₂ O ₄

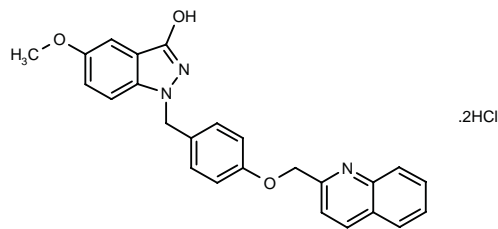
SOURCE – Meiji Milk.

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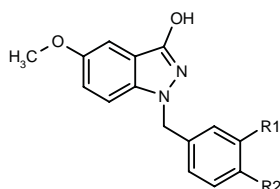
256152

5-Methoxy-1-[4-(quinolin-2-ylmethoxy)benzyl]indazol-3-ol dihydrochloride



C25-H21-N3-O3.2HCl; Mol wt: 484.38

ACTION – Antiallergic, antiinflammatory and immunomodulating agent, an inhibitor of 5-lipoxygenase ($IC_{50} = 44$ nM in rat macrophages) proven to inhibit ovalbumin-induced contractions of isolated tracheal tissue from sensitized guinea pigs ($IC_{50} = 2.9$ μ M). *In vivo* activity was demonstrated against ovalbumin-induced bronchoconstriction in sensitized guinea pigs, giving 45 and 70% inhibition at the doses of 5 and 10 mg/kg p.o., respectively; late-phase eosinophilia was also inhibited after ovalbumin challenge in the sensitized animals (46.0% inhibition at 10 mg/kg i.p.; 34.0% inhibition at 30 mg/kg p.o.). Other representative compounds within this series of specifically claimed 1,3,5-trisubstituted indazole derivatives include the following:



Compound	R1	R2	Formula
256992	H	OCH2Ph	C ₂₂ H ₂₀ N ₂ O ₃
256993	Cl	Cl	C ₁₅ H ₁₂ Cl ₂ N ₂ O ₂

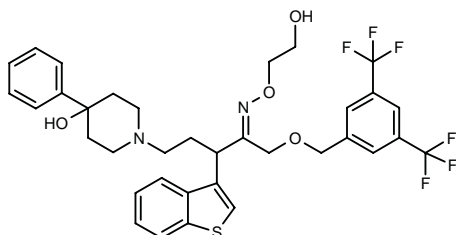
SOURCE – Arzneimittelwerk Dresden.

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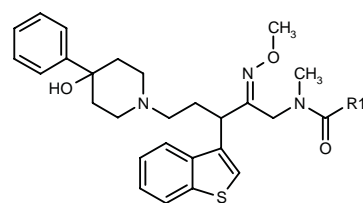
256844

3-(Benzo[*b*]thien-3-yl)-1-[3,5-bis(trifluoromethyl)benzyl-oxy]-5-(4-hydroxy-4-phenylpiperidin-1-yl)-2-pentanone O-(2-hydroxyethyl)oxime

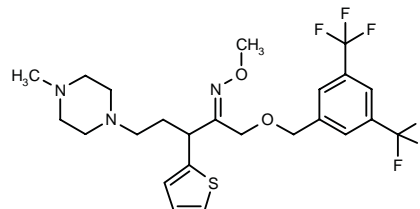


C35-H36-F6-N2-O4-S; Mol wt: 694.73

ACTION – Antiasthmatic and antiinflammatory agent, a dual neurokinin NK₁ and NK₂ receptor antagonist, as demonstrated in binding assays by K_i values of 1.8 and 23 nM, respectively, against [³H]-substance P and [³H]-neurokinin A binding in CHO cells transfected with human NK₁ and NK₂ receptors. A representative compound from a series of specifically claimed substituted oximes, hydrazones and olefins, wherein the following are also included:



Compound	R1	Formula
258014	3,5-(Me)2-Ph	C ₃₅ H ₄₁ N ₃ O ₃ S
258958	3,5-(CF ₃)2-PhNH	C ₃₅ H ₃₆ F ₆ N ₄ O ₃ S



258959: C24-H29-F6-N3-O2-S

SOURCE – Schering-Plough.

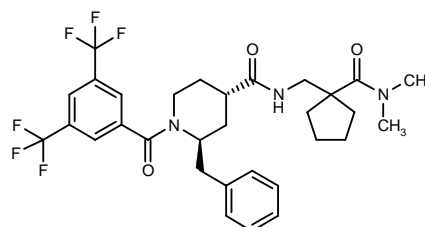
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CGP-73400

256854

2(*S*)-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-*N*-[1-(*N,N*-dimethylcarbamoyl)cyclopentylmethyl]piperidine-4(*S*)-carboxamide



C31-H35-F6-N3-O3; Mol wt: 611.63

ACTION – Potent, orally active, nonpeptide tachykinin NK₁ receptor antagonist ($IC_{50} = 13$ nM in bovine retina) with moderate activity at the NK₂ receptor ($IC_{50} = 123$ nM in CHO cells expressing the human receptor). In guinea pigs, it inhibited NK₁-mediated bronchospasm with an ED₅₀ of 0.19 mg/kg p.o. (2-h pretreatment) and NK₂-mediated bronchospasm by 42% at 10 mg/kg p.o. (2-h pretreatment).

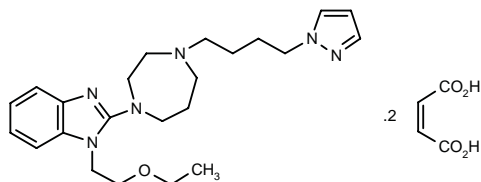
SOURCE – Novartis.

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254276

1-(2-Ethoxyethyl)-2-[4-[4-(pyrazol-1-yl)butyl]perhydro-1,4-diazepin-1-yl]benzimidazole dimaleate



C23-H34-N6-O.2C4-H4-O4; Mol wt: 642.71

ACTION – Antihistaminic (H_1) agent selected for further development from a new series of benzimidazoles. It was active in binding and functional studies *in vitro* ($K_i = 1.8$ nM against [3H]-mepyramine binding in guinea pig cerebral cortex; $pA_2 = 9.5$ for inhibition of histamine-induced contractions in guinea pig ileum) and *in vivo* against compound 48/80-induced mortality in rats ($ED_{50} = 0.03$ mg/kg i.p.). It appears to be devoid of sedative effects.

SOURCE – Esteve.

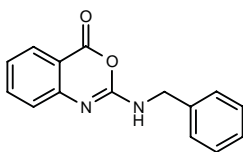
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TREATMENT OF RDS AND EMPHYSEMA

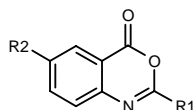
256788

2-(Benzylamino)-4*H*-3,1-benzoxazin-4-one



C15-H12-N2-O2; Mol wt: 252.27

ACTION – Potent acyl-enzyme inhibitor of human cathepsin G and bovine chymotrypsin ($K_i = 0.01$ μ M and 1.03 nM, respectively). Other 4*H*-3,1-benzoxazin-4-ones include the following:



Compound	R1	R2	Formula
256789	OCH2Ph	H	C ₁₅ H ₁₁ NO ₃
256790	OCH2Ph	Me	C ₁₆ H ₁₃ NO ₃
256791	N(Me)CH2Ph	H	C ₁₆ H ₁₄ N ₂ O ₂

Such compounds have been suggested to have potential in the treatment of inflammatory conditions such as adult respiratory distress syndrome, emphysema and arthritis.

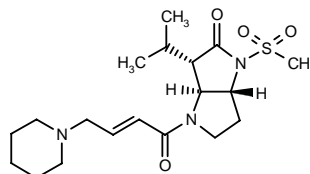
SOURCE – Novartis.

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257181

(3*S*,3*aS*,6*aR*)-3-Isopropyl-1-(methanesulfonyl)-4-[4-(1-piperidyl)-2(*E*)-butenoyl]perhydropyrrolo[3,2-*b*]pyrrol-2-one



C19-H31-N3-O4-S; Mol wt: 397.53

ACTION – Potent *in vitro* inhibitor of human neutrophil elastase (HNE; $IC_{50} = 0.022$ μ M) reported to protect against HNE-induced lung hemorrhage in hamsters at doses of less than 40 mg/kg intratracheally, with a duration of action of at least 6 h. Claimed for use in the treatment or prevention of chronic bronchitis and chronic obstructive pulmonary disease.

SOURCE – Glaxo Wellcome.

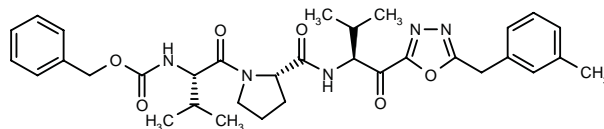
REFERENCES

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CE-2072

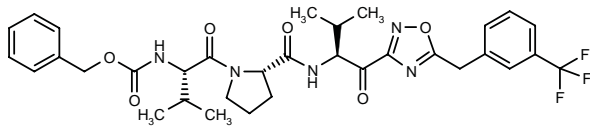
250867

5-(Benzyloxycarbonyl-L-valyl-L-prolyl-L-valyl)-2-(3-methylbenzyl)-1,3,4-oxadiazole



C33-H41-N5-O6; Mol wt: 603.72

ACTION – Orally active human neutrophil elastase (HNE) inhibitor ($K_i = 0.025$ nM) potentially useful for the treatment of elastase-mediated pulmonary diseases such as chronic bronchitis and emphysema. In a rat model of intratracheal HNE-induced acute lung hemorrhage, the drug induced a $46 \pm 17\%$ reduction in bronchoalveolar lavage hemoglobin content at a dose of 10 mg/kg p.o. and a $61 \pm 11\%$ reduction at a dose of 30 mg/kg p.o. using PEG-400 as the vehicle; when corn oil was used as the vehicle, it produced a $91 \pm 3\%$ reduction at a dose of 30 mg/kg. Another related compound is:



CE-2048 [250868]: C33-H38-F3-N5-O6

SOURCE – Cortech.

REFERENCES

1. Gyorkos, A. and Spruce, L.W. (Cortech, Inc.) *Human neutrophil elastase inhibitors*. EP 793674, WO 9616080.

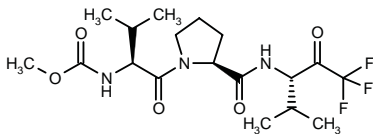
2. Selig, W. et al. *Comparison of orally active human neutrophil elastase inhibitors in a rat lung injury model*. Amer J Respir Crit Care Med 1997, 115(4, Part 2): A652.

3. Young, J. *Small molecule inhibitors of human neutrophil elastase*. IBC 2nd Int Conf Protease Inhib. Nov Ther Appl Dev (Feb 24-26, Washington DC) 1997.

ZD-8321*

240947

N-(Methoxycarbonyl)-L-valyl-L-prolyl-L-valyl-trifluoromethane



C18-H28-F3-N3-O5; Mol wt: 423.43

ACTION – Potent, orally active inhibitor of human leukocyte elastase (HLE; IC₅₀ = 13 ± 1.7 nM) with high selectivity over other enzymes. It exhibited potent activity in an acute elastase-induced hemorrhage model in hamsters (ED₅₀ = 0.51 mg/kg i.v., 2.0 mg/kg p.o.), inhibiting elastase-induced lung damage by 92% at 10 mg/kg p.o. The compound has high oral bioavailability in hamsters, rats and dogs (75, 84 and 70%, respectively) and potential in the treatment of cystic fibrosis, chronic bronchitis and acute respiratory distress syndrome (ARDS). It is currently undergoing clinical evaluation.

SOURCE – Zeneca.

REFERENCES

1. Bernstein, P.R. et al. (Zeneca, Ltd.) *Proline derivs. useful as inhibitors of human leukocyte elastase*. EP 808327, WO 9623812.

2. Veale, C.A. et al. *Orally active trifluoromethyl ketone inhibitors of human leukocyte elastase*. J Med Chem 1997, 40(20): 3173.

3. *87 development projects under way at Zeneca*. Prous Science Daily Essentials December 16, 1997.

4. Zeneca Group plc R&D Presentation (Dec 12, London) 1995.

5. Zeneca Pharmaceuticals Annual Report and Accounts 1995.

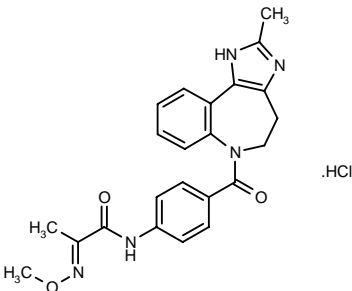
*Identified compound **240947** Annu Drug Data Rep 1996, 18(11): 973.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

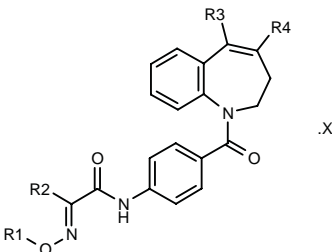
255511

2-(Methoxyimino)-*N*-[4-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepin-6-ylcarbonyl)phenyl]propionamide hydrochloride

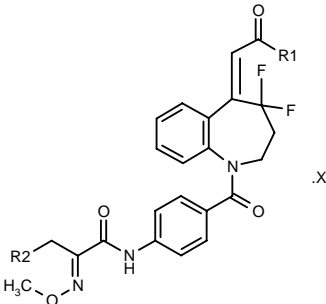


C23-H23-N5-O3.HCl; Mol wt: 453.93

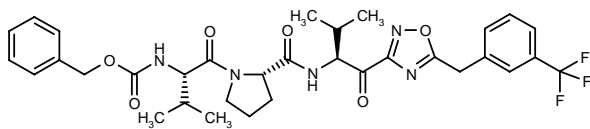
ACTION – Selective vasopressin V₁ antagonist potentially useful as an antihypertensive agent. At doses of 1-10 mg/kg p.o., the compound inhibited the pressor response elicited by arginine vasopressin (AVP) in rats. Within this series of oxime derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
257029	Et	Et	-NHC(Me)=N-		HCl	C ₂₅ H ₂₇ N ₅ O ₃ .HCl
257030	Me	i-Pr	-NHC(Me)=N-		HCl	C ₂₅ H ₂₇ N ₅ O ₃ .HCl
257034	Me	Et	-NHC(2-Pyr-CH2)=N-			C ₂₉ H ₂₈ N ₆ O ₃
257035	Me	Et	-N=C(Pr)-S-			C ₂₆ H ₂₈ N ₄ O ₃ S
257036	Me	Et	-N=C(4-Pyr-CH2)-S-			C ₂₆ H ₂₇ N ₅ O ₃ S
257037	Me	Et	-O-C(Et)=N-			C ₂₅ H ₂₆ N ₄ O ₄



Compound	R1	R2	X	Formula
257031	4-morpholinyl	H	HCl	C ₂₇ H ₂₈ F ₂ N ₄ O ₅ .HCl
257032	4-Pyr-NH	H		C ₂₈ H ₂₅ F ₂ N ₅ O ₄
257033	4-morpholinyl	Me		C ₂₈ H ₃₀ F ₂ N ₄ O ₅



CE-2048 [250868]: C33-H38-F3-N5-O6

SOURCE – Cortech.

REFERENCES

1. Gyorkos, A. and Spruce, L.W. (Cortech, Inc.) *Human neutrophil elastase inhibitors*. EP 793674, WO 9616080.

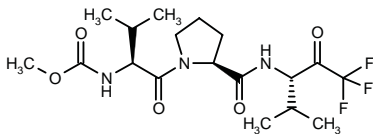
2. Selig, W. et al. *Comparison of orally active human neutrophil elastase inhibitors in a rat lung injury model*. Amer J Respir Crit Care Med 1997, 115(4, Part 2): A652.

3. Young, J. *Small molecule inhibitors of human neutrophil elastase*. IBC 2nd Int Conf Protease Inhib. Nov Ther Appl Dev (Feb 24-26, Washington DC) 1997.

ZD-8321*

240947

N-(Methoxycarbonyl)-L-valyl-L-prolyl-L-valyl-trifluoromethane



C18-H28-F3-N3-O5; Mol wt: 423.43

ACTION – Potent, orally active inhibitor of human leukocyte elastase (HLE; IC₅₀ = 13 ± 1.7 nM) with high selectivity over other enzymes. It exhibited potent activity in an acute elastase-induced hemorrhage model in hamsters (ED₅₀ = 0.51 mg/kg i.v., 2.0 mg/kg p.o.), inhibiting elastase-induced lung damage by 92% at 10 mg/kg p.o. The compound has high oral bioavailability in hamsters, rats and dogs (75, 84 and 70%, respectively) and potential in the treatment of cystic fibrosis, chronic bronchitis and acute respiratory distress syndrome (ARDS). It is currently undergoing clinical evaluation.

SOURCE – Zeneca.

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1. Bernstein, P.R. et al. (Zeneca, Ltd.) *Proline derivs. useful as inhibitors of human leukocyte elastase*. EP 808327, WO 9623812.

2. Veale, C.A. et al. *Orally active trifluoromethyl ketone inhibitors of human leukocyte elastase*. J Med Chem 1997, 40(20): 3173.

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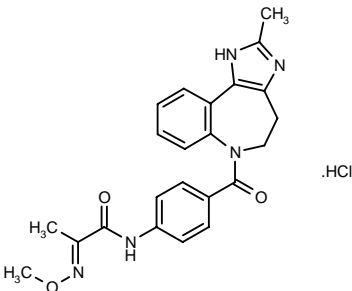
*Identified compound **240947** Annu Drug Data Rep 1996, 18(11): 973.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

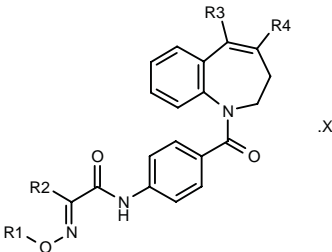
255511

2-(Methoxyimino)-*N*-[4-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepin-6-ylcarbonyl)phenyl]propionamide hydrochloride

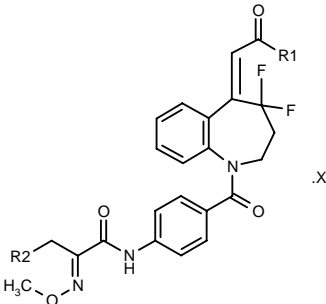


C23-H23-N5-O3.HCl; Mol wt: 453.93

ACTION – Selective vasopressin V₁ antagonist potentially useful as an antihypertensive agent. At doses of 1-10 mg/kg p.o., the compound inhibited the pressor response elicited by arginine vasopressin (AVP) in rats. Within this series of oxime derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
257029	Et	Et	-NHC(Me)=N-		HCl	C ₂₅ H ₂₇ N ₅ O ₃ .HCl
257030	Me	i-Pr	-NHC(Me)=N-		HCl	C ₂₅ H ₂₇ N ₅ O ₃ .HCl
257034	Me	Et	-NHC(2-Pyr-CH2)=N-			C ₂₉ H ₂₈ N ₆ O ₃
257035	Me	Et	-N=C(Pr)-S-			C ₂₆ H ₂₈ N ₄ O ₃ S
257036	Me	Et	-N=C(4-Pyr-CH2)-S-			C ₂₈ H ₂₇ N ₅ O ₃ S
257037	Me	Et	-O-C(Et)=N-			C ₂₅ H ₂₆ N ₄ O ₄



Compound	R1	R2	X	Formula
257031	4-morpholinyl	H	HCl	C ₂₇ H ₂₈ F ₂ N ₄ O ₅ .HCl
257032	4-Pyr-NH	H		C ₂₈ H ₂₅ F ₂ N ₅ O ₄
257033	4-morpholinyl	Me		C ₂₈ H ₃₀ F ₂ N ₄ O ₅

SOURCE – Yamanouchi.

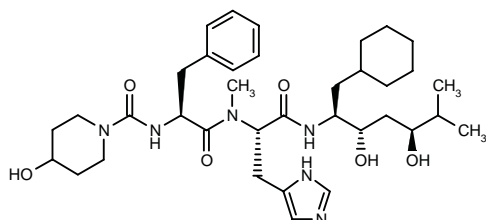
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JTP-2724

256082

4-Hydroxypiperidin-1-ylcarbonyl-L-phenylalanyl-(*N*^α-methyl)histidine 1(*S*)-(cyclohexylmethyl)-2(*S*),4(*S*)-dihydroxy-5-methylhexylamide



C36-H56-N6-O6; Mol wt: 668.88

ACTION – Antihypertensive agent, a potent and selective inhibitor of renin (IC_{50} = 0.68, 1.2 and 0.52 nM, respectively, against human, cynomolgus monkey and marmoset plasma renin) with no activity against porcine pepsin, bovine cathepsin D or human angiotensin-converting enzyme (ACE; IC_{50} > 100,000 nM). Oral administration (5 or 10 mg/kg) of the compound in salt-depleted, conscious marmosets produced a significant and long-lasting reduction in systolic blood pressure.

SOURCES – Japan Tobacco; Yoshitomi.

REFERENCES

1. Uchida, I. et al. (Japan Tobacco, Inc.; Yoshitami Pharm. Ind., Ltd.) *Novel amino acid derivs. possessing renin-inhibitory activities.* EP 396065, JP 91204860.
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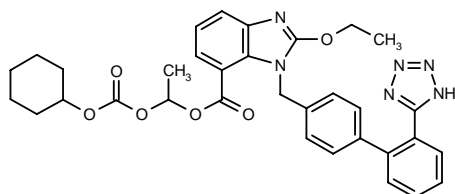
CANDESARTAN CILEXETIL

Prop INN

179243

(±)-2-Ethoxy-1-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-1*H*-benzimidazole-7-carboxylic acid 1-(cyclohexyloxycarbonyloxy)ethyl ester

H212/91
TCV-116⁺



C33-H34-N6-O6; Mol wt: 610.67

ACTION – Long-acting angiotensin II AT₁ receptor antagonist.

INDICATION – Treatment of essential hypertension.

PRESENTATION – Tablets, 4, 8 and 16 mg.

PROPRIETARY NAMES– *Amias* (GB); *Atacand* (SE); *Blopress* (DE).

SOURCES – Discovered by Takeda; comarketed in most countries with Astra (Sweden: Astra only).

RECENT REFERENCES

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6. Forsblom, C. et al. *Candesartan cilexetil, a novel angiotensin II antagonist reduces microalbuminuria in patients with type II diabetes mellitus and mild hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst P3.91.
7. Franke, H. et al. *Comparison of the efficacy and safety of candesartan cilexetil 4, 8 and 12 mg with placebo and enalapril 10 mg in patients with mild to moderate essential hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst 99.
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9. Kohara, K. et al. *Effect of AT₁ receptor blockade with candesartan cilexetil (TCV-116) on twenty four hour blood pressure in essential hypertension.* Amer J Hypertension 1997, 10(4, Part 2): 171A.
10. MacGregor, G.A. et al. *The efficacy of candesartan cilexetil: An angiotensin II type I receptor antagonist alone or in combination with amlodipine or in combination with amlodipine and hydrochlorothiazide in patients with moderate-to-severe essential hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst 192.
11. Maeda, Y. et al. *Comparison of the therapeutic effects of long-term administration with an angiotensin II receptor antagonist (TCV-116) and an ACE inhibitor in congestive heart failure.* Jpn Circ J 1997, 61(Suppl. 1): Abst 1074.
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13. McInnes, G.T. and Jonker, J. *Antihypertensive effects and tolerability of candesartan cilexetil in an elderly population.* J Hypertension 1997, 15(Suppl. 4): Abst P3.105.
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20. Trenkwalder, P. et al. *Long-term treatment with candesartan cilexetil does not affect glucose homeostasis or serum lipid profile in patients with mild hypertension and type II diabetes.* J Hypertension 1997, 15(Suppl. 4): Abst 372.

21. Yusuf, S. et al. *Effects of candesartan, enalapril or their combination on exercise capacity, ventricular function, clinical deterioration and quality of life in heart failure: Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD)*. Circulation 1997, 96(8, Suppl.): Abst 2527.

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24. *Atacand launched in Sweden*. Prous Science Daily Essentials November 13, 1997.

25. *Candesartan introduced in U.K., Germany*. Prous Science Daily Essentials December 5, 1997.

26. *Major innovations fuel R&D at Astra*. Prous Science Daily Essentials January 28, 1998.

27. *Mutual recognition approval obtained for Astra's angiotensin II blocker*. Prous Science Daily Essentials October 9, 1997.

28. *Takeda's Atacand scheduled for European launch later this year*. Prous Science Daily Essentials July 22, 1997.

29. *Takeda's Blopess approved in EC*. Prous Science Daily Essentials October 16, 1997.

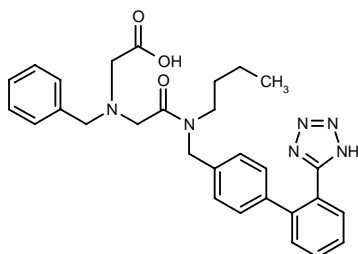
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*Annu Drug Data Rep 1993, 15(3): 246.

TH-142177

256850

N-Benzyl-*N*-[2-[*N*-butyl-*N*-(2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]-2-oxoethyl]glycine



C29-H32-N6-O3; Mol wt: 512.61

ACTION – Orally active antihypertensive agent, a potent and selective angiotensin II (AII) AT₁ receptor antagonist with a long duration of action after oral dosing. In isolated rat aorta, it was approximately 3 times more potent than losartan in inhibiting AII-induced contractions ($pA_2 = 9.07$), and it potently inhibited [¹²⁵I]-AII binding to AT₁ receptors in rat aortic membranes ($K_i = 16$ nM), whereas it did not affect [¹²⁵I]-AII binding to AT₂ receptors in membranes from bovine cerebellum or human myocardium. In anesthetized normotensive rats, it significantly and dose-dependently ($ID_{50} = 2.80$ μ mol/kg i.v.) inhibited the AII-induced pressor response, being 1.5 times less potent than losartan ($ID_{50} = 1.91$ μ mol/kg i.v.). Upon oral administration (0.6-5.5 μ mol/kg) to renal hypertensive, rats, it dose-dependently reduced systolic blood pressure without affecting heart rate, with a significant effect for at least 24 h after the highest dose; the extent and duration of the antihypertensive effect were greater than for losartan (6.5 μ mol/kg).

SOURCE – Taiho.

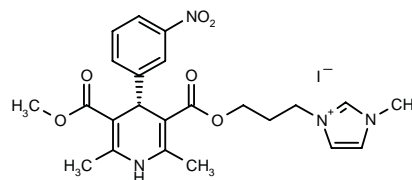
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2. Nozawa, Y. et al. *Pharmacological profile of TH-142177, a novel orally active AT₁-receptor antagonist*. Fundam Clin Pharmacol 1997, 11(5): 395.

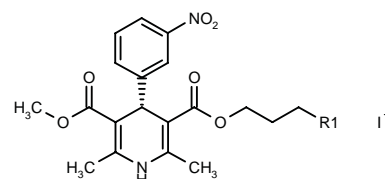
255073

3-[3-[5-(Methoxycarbonyl)-2,6-dimethyl-4(*S*)-(3-nitrophenyl)-1,4-dihydropyridin-3-ylcarbonyloxy]propyl]-1-methylimidazolium iodide



C23-H27-I-N4-O6; Mol wt: 582.39

ACTION – Antihypertensive and vasodilating agent, a dihydropyridine derivative shown to inhibit calcium-induced rat aorta contractions with an IC_{50} value of 1.8 pmol/l and reported to possess excellent water solubility. Other compounds from this series of optically active 1,4-dihydropyridine derivatives include the following:



Compound	R1	Formula
257834	1-Pyr	C ₂₄ H ₂₆ IN ₃ O ₆
257835	3-thiazolyl	C ₂₂ H ₂₄ IN ₃ O ₆ S
257836	2-pyridazinyl	C ₂₃ H ₂₅ IN ₄ O ₆
257837	3-(CO ₂ Me)-1-Pyr	C ₂₆ H ₂₈ IN ₃ O ₈
257838	3-CN-1-Pyr	C ₂₅ H ₂₅ IN ₄ O ₆
257839	4-N(Me)2-1-Pyr	C ₂₆ H ₃₁ IN ₄ O ₆
257841	3-(CONH ₂)-1-Pyr	C ₂₅ H ₂₇ IN ₄ O ₇
257843	1-Me-3-Pyr	C ₂₅ H ₂₈ IN ₃ O ₆

SOURCE – Mercian.

REFERENCES

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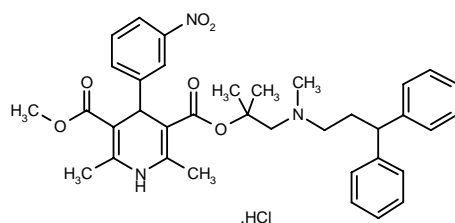
LERCANIDIPINE HYDROCHLORIDE

Rec INN; BANM

090990

(±)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-[N-(3,3-diphenylpropyl)-N-methylamino]-1,1-dimethylethyl methyl diester hydrochloride

Rec-15/2375+
TJN-324



C36-H41-N3-O6.HCl; Mol wt: 648.20

ACTION – Long-lasting vasoselective calcium antagonist with a gradual onset of activity.

INDICATION – Treatment of hypertension.

PRESENTATION – Tablets, 10 mg (9.4 mg lercanidipine).

PROPRIETARY NAME – *Lerdip* (NL).

SOURCES – Recordati; marketed by Byk Nederland (Byk Gulden).

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15. Sironi, G. et al. *Antihypertensive effects of lercanidipine in experimental hypertensive rats and dogs.* Arzneimittel-Forsch-Drug Res 1996, 46(2): 145.

16. Sironi, G. et al. *Haemodynamic effects of lercanidipine in anaesthetized open-chest dogs.* Arzneimittel-Forsch-Drug Res 1996, 46(3): 256.

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18. *Lercanidipine launch.* Recordati Industria Chimica Farmaceutica SPA Company Communication 1997, October 30.

19. *Lercanidipine: New licensing-out agreements for Italy, Spain, Belgium and Luxembourg.* Recordati Industria Chimica Farmaceutica SPA Press Release 1997, November 10.

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21. *Recordati's lercanidipine launched in The Netherlands.* Prous Science Daily Essentials October 31, 1997.

22. *Recordati signs licensing agreement with Zeneca, Zambon and Rotta for lercanidipine.* Prous Science Daily Essentials November 11, 1997.

23. *The new calcium antagonist lercanidipine: Coupling efficacy and safety for best compliance.* Recordati Industria Chimica Farmaceutica SPA Press Release 1997, October 30.

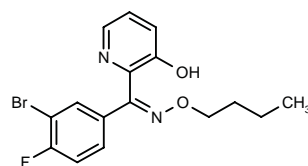
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MONOGRAPH – Bianchi, G. and Leonardi, A. *REC 15/2375.* Drugs Fut 1987, 12(12): 1113.

*Annu Drug Data Rep 1986, 8(10): 920.

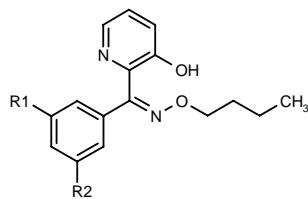
256348

1-(3-Bromo-4-fluorophenyl)-1-(3-hydroxypyridin-2-yl)methanone O-butyloxime

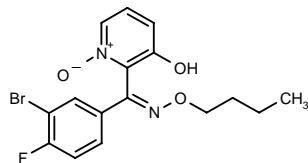


C16-H16-Br-F-N2-O2; Mol wt: 367.22

ACTION – Antihypertensive and antianginal agent, a potassium channel opener with smooth muscle relaxant activity, as demonstrated by marked inhibition of tetraethyl ammonium chloride + BaCl₂-induced contractions of rat aorta preparations (87% inhibition at 0.1 μM), whereas it had a negligible inhibitory effect against contractions elicited by 80 mM KCl. In anesthetized dogs, test compound increased coronary blood flow by 136% at 30 μg administered into the coronary artery. Compound caused a significant decrease in blood pressure in spontaneously hypertensive rats at a dose of 0.3 mg/kg p.o, whereas its effect in normotensive rats was negligible; in both animals the effect on heart rate was not statistically significantly different from controls. Other specifically claimed hydroxypyridine derivatives include the following:



Compound	R1	R2	Formula
256982	Br	H	C ₁₆ H ₁₇ BrN ₂ O ₂
256983	Cl	Cl	C ₁₆ H ₁₆ Cl ₂ N ₂ O ₂
256984	CF ₃	H	C ₁₇ H ₁₇ F ₃ N ₂ O ₂
256985	NO ₂	H	C ₁₆ H ₁₇ N ₃ O ₄



256986: C16-H16-Br-F-N2-O3

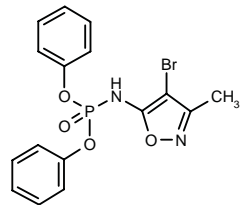
SOURCE – Takeda.

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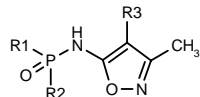
256213

N-(4-Bromo-3-methyl-5-isoxazolyl)phosphoramidic acid diphenyl ester



C16-H14-Br-N2-O4-P; Mol wt: 409.18

ACTION – Antihypertensive agent, an endothelin receptor antagonist with higher affinity for ET_A receptors than ET_B receptors (IC₅₀ = 0.58 and 77 μM, respectively). Other specifically claimed phosphoramidates and phosphinic amides include the following:



Compound	R1=R2	R3	Formula
257469	OEt	Br	C ₈ H ₁₄ BrN ₂ O ₄ P
257470	OPh	Me	C ₁₇ H ₁₇ N ₂ O ₄ P
257471	Ph	Me	C ₁₇ H ₁₇ N ₂ O ₂ P
257472	Ph	Br	C ₁₆ H ₁₄ BrN ₂ O ₂ P

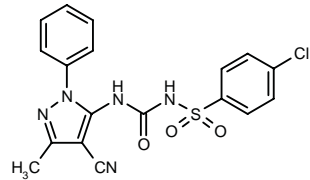
SOURCE – Texas Biotechnology.

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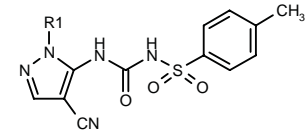
255069

N-(4-Chlorophenylsulfonyl)-N'-(4-cyano-3-methyl-1-phenylpyrazol-5-yl)urea



C18-H14-Cl-N5-O3-S; Mol wt: 415.85

ACTION – Agent for the treatment or prevention of hypertension, circulatory disorders, bronchospasm, ulcers and vascular lesions with endothelin-converting enzyme (ECE)-inhibitory activity (IC₅₀ = 45 nM against enzyme from rat lung preparations). *In vivo*, it inhibited the big endothelin-1-induced pressor response in rats at doses of 3 and 10 mg/kg i.v. Other compounds from this series of sulfonylureidopyrazole derivatives include the following:



Compound	R1	Formula
257844	Ph	C ₁₈ H ₁₅ N ₅ O ₃ S
257845	cyclohexyl	C ₁₈ H ₂₁ N ₅ O ₃ S

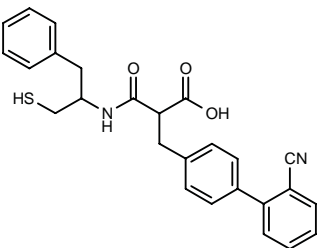
SOURCE – Sumitomo.

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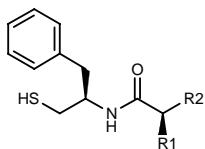
255659

N-(1-Benzyl-2-sulfanylethyl)-2-(2'-cyanobiphenyl-4-ylmethyl)malonic acid



C26-H24-N2-O3-S; Mol wt: 444.55

ACTION – Antihypertensive and antiischemic agent, an endothelin-converting enzyme (ECE) inhibitor (IC₅₀ = 30 nM). Other specifically claimed sulfur derivatives include the following:



Compound	R1	R2	Formula
256794	3-indolyl-CH2	NHCO2CH2Ph	C ₂₈ H ₂₉ N ₃ O ₃ S
256795	H	(CH2)9OPh	C ₂₈ H ₃₇ NO ₂ S

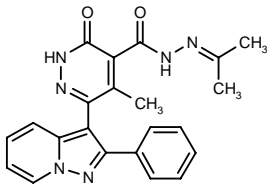
SOURCE – Hoechst Marion Roussel.

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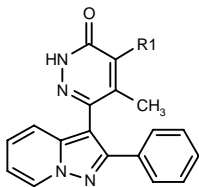
255503

5-Methyl-3-oxo-6-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)-2,3-dihydropyridazine-4-carboxylic acid *N*²-isopropylidenehydrazide



C22-H20-N6-O2; Mol wt: 400.44

ACTION – Adenosine antagonist with potential in the treatment of hypertension, heart failure, renal failure and as a diuretic agent, a representative compound from a series of pyrazolo[1,5-a]pyridine derivatives, wherein the following are also included:



Compound	R1	Formula
257270	CO2H	C ₁₉ H ₁₄ N ₄ O ₃
257271	H	C ₁₈ H ₁₄ N ₄ O
257272	CH2COMe	C ₂₁ H ₁₈ N ₄ O ₂

SOURCE – Fujisawa.

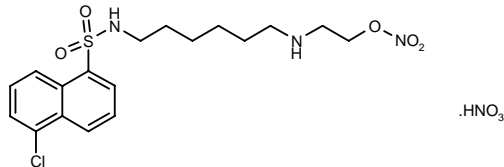
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

255492

5-Chloro-*N*-[6-(2-nitrooxyethylamino)hexyl]naphthalene-1-sulfonamide nitrate



C18-H24-Cl-N3-O5-S.H-N-O3; Mol wt: 492.93

ACTION – Nitrovasodilator and smooth muscle cell proliferation inhibitor, potentially useful in the treatment of angina pectoris and in the prevention of restenosis following percutaneous transluminal coronary angioplasty (PTCA). *In vitro*, compound induced 52% inhibition of the proliferation of rat aortic smooth muscle cells at 10 μM; at this concentration, it completely inhibited 3,4-diaminopyridine-induced rhythmic contractions in isolated rabbit aorta.

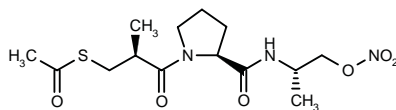
SOURCE – Chugai.

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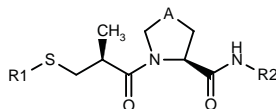
255613

1-[3-(Acetylsulfanyl)-2(*S*)-methylpropionyl]-*N*-[1(*S*)-methyl-2-(nitrooxy)ethyl]-L-prolinamide



C14-H23-N3-O6-S; Mol wt: 361.41

ACTION – Agent for the treatment or prevention of angina pectoris with excellent vasodilating properties. A representative compound from a series of thiazolidine derivatives, wherein the following are also included:



Compound	R1	R2	A	Formula
257335	H	CH(Me)CH2ONO2	CH2	C ₁₂ H ₂₁ N ₃ O ₅ S
257336	Ac	(R)-CH(Me)CH2ONO2	CH2	C ₁₄ H ₂₃ N ₃ O ₅ S
257337	Ac	trans-4-(CH2ONO2)-cyclohexyl-CH2	S	C ₁₈ H ₂₉ N ₃ O ₆ S ₂
257338	Ac	(S)-CH(Me)CH2ONO2	O	C ₁₃ H ₂₁ N ₃ O ₇ S
257339	Ac	trans-4-(CH2ONO2)-cyclohexyl-CH2	O	C ₁₈ H ₂₉ N ₃ O ₇ S
257340	Ac	(S)CH(Pr)CH2ONO2	O	C ₁₅ H ₂₅ N ₃ O ₇ S
257341	Ac	(S)-CH(Me)CH2ONO2	S	C ₁₃ H ₂₁ N ₃ O ₆ S ₂

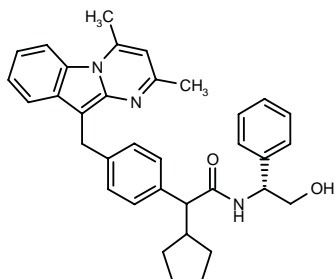
SOURCE – Sankyo.

REFERENCES

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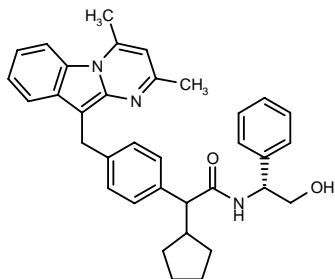
256334

2-Cyclopentyl-2-[4-(2,4-dimethylpyrimido[1,2-*a*]indol-10-ylmethyl)phenyl]-*N*-[2-hydroxy-1(*R*)-phenylethyl]-acetamide



C35-H37-N3-O2; Mol wt: 531.70

ACTION – Agent for the treatment of atherosclerosis that inhibits intestinal triglyceride absorption *in vivo* in rats and VLDL secretion *in vivo* in hamsters, and the release of apolipoprotein B-100-associated lipoproteins in HepG2 cells. Other representative compounds within this series of pyrimido[1,2-*a*]indoles include the following:



Compound	Isomer	Formula
257096	S	C ₃₅ H ₃₇ N ₃ O ₂
257097	R	C ₃₅ H ₃₇ N ₃ O ₂

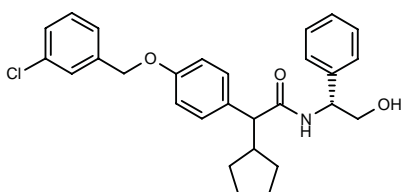
SOURCE – Bayer.

REFERENCES

1. Müller, U. et al. (Bayer AG) *Pyrimido[1,2-*a*]indoles.* DE 19613550, EP 799828.

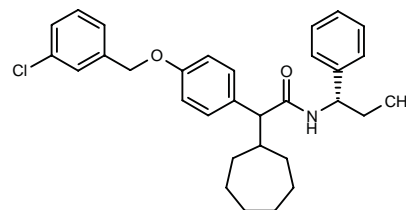
256347

2-[4-(3-Chlorobenzoyloxy)phenyl]-2-cyclopentyl-*N*-[2-hydroxy-1(*R*)-phenylethyl]acetamide



C28-H30-Cl-N-O3; Mol wt: 464.00

ACTION – Antiatherosclerotic agent with antiproliferative activity that inhibits the release of apolipoprotein B-100-associated lipoproteins, thus causing a reduction in plasma VLDL levels. Another compound from this series of benzoyl-substituted phenylglycinolamide derivatives is:



257120: C31-H36-Cl-N-O2

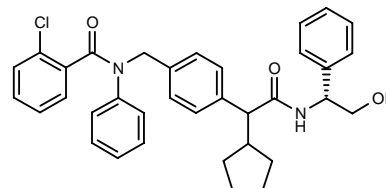
SOURCE – Bayer.

REFERENCES

1. Goldmann, S. et al. (Bayer AG) *Benzoyloxy-subst. phenylglycinolamides as pharmaceutical agents.* DE 19615263, EP 802186.

256349

2-[4-(2-Chloro-*N*-phenylbenzamidomethyl)phenyl]-2-cyclopentyl-*N*-[2-hydroxy-1(*R*)-phenylethyl]acetamide



C35-H35-Cl-N2-O3; Mol wt: 567.13

ACTION – Antiatherosclerotic agent with antiproliferative activity and which inhibits the release of apolipoprotein B-100-associated lipoproteins, thus causing a reduction in plasma VLDL levels.

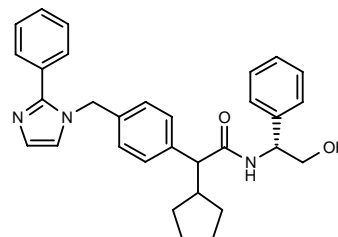
SOURCE – Bayer.

REFERENCES

1. Goldmann, S. et al. (Bayer AG) *Phenylglycinolamides linked by a hetero-atom with antiatherosclerotic agents.* DE 19615262, EP 802188.

256350

2-Cyclopentyl-*N*-[2-hydroxy-1(*R*)-phenylethyl]-2-[4-(2-phenylimidazol-1-ylmethyl)phenyl]acetamide



C31-H33-N3-O2; Mol wt: 479.62

ACTION – Antiatherosclerotic agent with antiproliferative activity and which inhibits the release of apolipoprotein B-100-associated lipoproteins, thus causing a reduction in plasma VLDL levels.

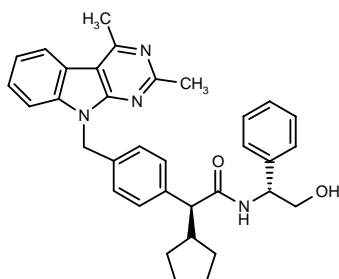
SOURCE – Bayer.

REFERENCES

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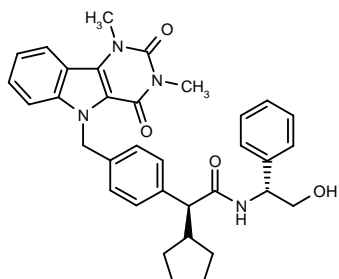
256354

2(S)-Cyclopentyl-2-[4-(2,4-dimethyl-9H-pyrimido[4,5-b]-indol-9-ylmethyl)phenyl]-N-[2-hydroxy-1(R)-phenylethyl]acetamide

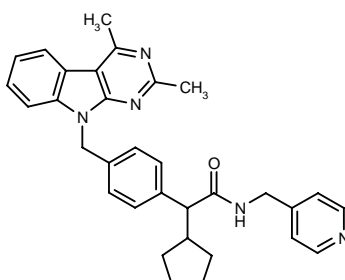


C34-H36-N4-O2; Mol wt: 532.68

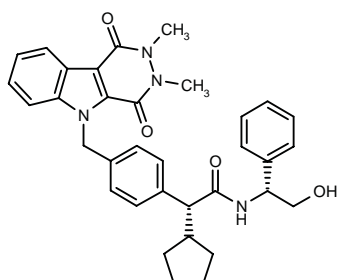
ACTION – Antiatherosclerotic agent with antiproliferative activity proven to inhibit the release of apolipoprotein B-100-associated lipoproteins from HepG2 cells (IC_{50} = 0.8 nM). A representative compound from a series of pyridazino-, pyrimido-, pyrazino- and triazino-indoles, wherein the following are also included:



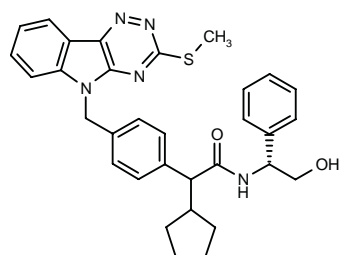
257121: C34-H36-N4-O4



257122: C32-H33-N5-O



257123: C34-H36-N4-O4



257124: C32-H33-N5-O2-S

SOURCE – Bayer.

REFERENCES

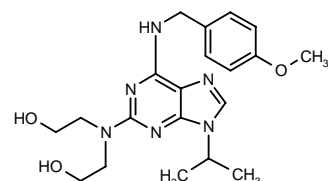
1. Müller, U. et al. (Bayer AG) *Pyridazino-, pyrimido-, pyrazino and triazino-indoles*. EP 802198.

CVT-313

256881

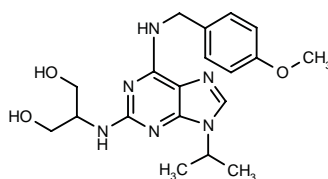
*N*²,*N*²-Bis(2-hydroxyethyl)-9-isopropyl-*N*⁶-(4-methoxybenzyl)purine-2,6-diamine

2-[*N,N*-Bis(2-hydroxyethyl)amino]-9-isopropyl-6-(4-methoxybenzylamino)purine



C20-H28-N6-O3; Mol wt: 400.48

ACTION – Antiproliferative agent, a potent, selective and competitive inhibitor of cyclin-dependent kinase 2 (CDK2; IC_{50} = 0.5 μ M, K_i = 95 nM). It inhibited the proliferation of a number of mouse, rat and human cell lines including murine and human tumor cell lines, human lung fibroblasts and rat neonatal aortic smooth muscle cells, with IC_{50} values of 1.25-20 μ M. The compound was effective in a rat model of carotid artery restenosis, reducing neointima formation by 80% after exposure of the denuded carotid artery to 1.25 mg/kg of the hydrochloride salt. Another compound from this series of 2,6,9-trisubstituted purines is:



256882: C19-H26-N6-O3

SOURCE – CV Therapeutics.

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2. Schow, S.R. et al. *Synthesis and activity of 2,6,9-trisubstituted purines*. Bioorg Med Chem Lett 1997, 7(21): 2697.

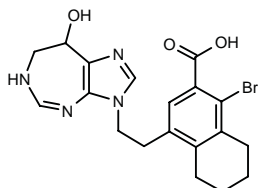
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4. CV Therapeutics Annual Report 1996.

GP-3789

254534

1-Bromo-4-[2-(8-hydroxy-3,6,7,8-tetrahydroimidazo[4,5-d][1,3]diazepin-3-yl)ethyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid



C19-H21-Br-N4-O3; Mol wt: 433.30

ACTION – A highly potent and selective inhibitor of adenosine 5'-monophosphate deaminase (AMPDA; $K_i = 3$ nM in human erythrocytes) with > 30,000-fold selectivity over adenosine deaminase.

AMPDA has been implicated as a potential target for antiischemic drugs (cardioprotective and neuroprotective agents) based on the theory that enzyme activity in ischemic tissues directs the ATP degradation product AMP to nonadenylates, thereby reducing the production of adenosine.

SOURCE – Metabasis Therapeutics.

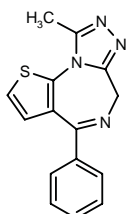
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RO-11-1464

256577

9-Methyl-4-phenyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a]-[1,4]diazepine



C15-H12-N4-S; Mol wt: 280.35

ACTION – Antiatherosclerotic agent, a thienotriazolobenzodiazepine able to increase the production of apolipoprotein A-I (apoA-I) in HepG2 cells and to increase apoA-I levels in hamsters by 40% at 30 mg/kg/day in the food for 10 days, with no effect on apolipoprotein B (apo-B) or triglyceride levels. Compound has weak or no activity on central benzodiazepine receptors.

SOURCE – Roche.

REFERENCES

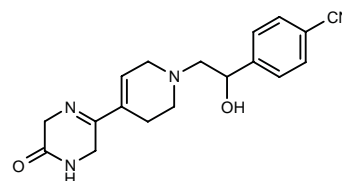
1. Hellerbach, J. et al. (F. Hoffmann-La Roche AG) *Diazepine derivs*. DE 2405682.
2. Kempen, H. (F. Hoffmann-La Roche AG) *Use of thienotriazolodiazepine to increase apolipoprotein A-I levels*. WO 9709048.
3. Kempen, H.J. *A thienotriazolobenzodiazepine (Ro 11-1464) increases production of apolipoprotein A-I by Hep-G2 cells, and elevates its plasma concentration in the hamster*. Circulation 1997, 96(8, Suppl.): Abst 2706.

HEART FAILURE THERAPY

SCH00013

256578

4-[1-Hydroxy-2-[4-(5-oxo-3,4,5,6-tetrahydropyrazin-2-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]benzonitrile



C18-H20-N4-O2; Mol wt: 324.38

ACTION – Cardiotonic agent with little chronotropic activity, a pyridazinone derivative shown to produce a concentration-dependent positive inotropic effect in isolated canine ventricular muscle and rabbit papillary muscle; it appears to act via cAMP-dependent mechanisms and an increase in myofibrillar Ca^{2+} sensitivity. Potentially useful in the treatment of heart failure.

SOURCE – Yamagata Univ., Yamagata (JP).

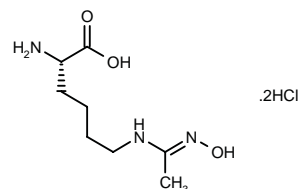
REFERENCES

1. Sugawara, H. and Endoh, M. *Effects of SCH00013, a cardiotonic pyridazinone derivative, on mammalian cardiac muscle*. Circulation 1997, 96(8, Suppl.): Abst 762.

MISCELLANEOUS CARDIOVASCULAR DRUGS

255655

*N*⁶-[1-(Hydroxyimino)ethyl]-L-lysine dihydrochloride



C8-H17-N3-O3.2HCl; Mol wt: 276.16

ACTION – Nitric oxide synthase (NOS) inhibitor giving IC_{50} values of 154, 1474 and 907 μ M against recombinant human inducible NOS (iNOS), recombinant human endothelial constitutive NOS (ecNOS) and recombinant human neuronal constitutive NOS (ncNOS), respectively. It inhibited lipopolysaccharide (LPS)-induced NOS production in RAW 264.7 cells ($IC_{50} = 28$ μ M). *In vivo*, it reduced plasma nitrite levels in rats treated with LPS, with 54 and 97% inhibition, respectively, at 1 and 10 mg/kg/day p.o. A representative compound within a series of specifically claimed hydroxyamidino derivatives.

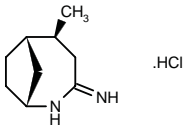
SOURCE – Searle.

REFERENCES

1. Gapud, R.E. et al. (G.D. Searle & Co.) *Hydroxyamidino derivs. useful as nitric oxide synthase inhibitors*. WO 9732844.

255720

exo-5-Methyl-2-azabicyclo[4.2.1]nonan-3-imine hydrochloride



C9-H16-N2.HCl; Mol wt: 188.70

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the inducible isoform over the constitutive isoform (IC₅₀ = 0.133 and 82.3 μM against inducible NOS [iNOS] from mouse macrophages and human endothelial constitutive NOS [ecNOS], respectively). Potentially useful in the treatment or prevention of shock, hypotension, rheumatoid arthritis, ulcerative colitis, cerebral ischemia, insulin-dependent diabetes mellitus and cancer.

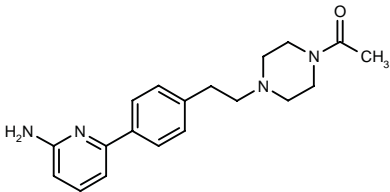
SOURCE – Ono.

REFERENCES

1. Taniguchi, N. et al. (Ono Pharm. Co., Ltd.) *Nitric oxide synthase inhibitors*. JP 97208562.

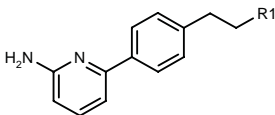
257157

6-[4-[2-(4-Acetylpiperazin-1-yl)ethyl]phenyl]pyridin-2-ylamine



C19-H24-N4-O; Mol wt: 324.42

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment of septic shock, CNS disorders and inflammatory disorders. Within this series of specifically claimed 6-phenylpyridin-2-ylamine derivatives, the following are also included:



Compound	R1	Formula
258142	6-NH2-3-azabicyclo[3.1.0]hex-3-yl	C ₁₈ H ₂₂ N ₄
258143	4-(PhCH2CH2)-1-Piz	C ₂₅ H ₃₀ N ₄
258144	4-[PhCH(OH)CH2]-1-Piz	C ₂₅ H ₃₀ N ₄ O
258145	3-(4-F-PhCH2CONH)-1-pyrrolidinyl	C ₂₅ H ₂₇ FN ₄ O

SOURCE – Pfizer.

REFERENCES

1. Lowe, J.A. III and Whittle, P.J. (Pfizer, Inc.) *6-Phenylpyridyl-2-amine derivs*. WO 9736871.

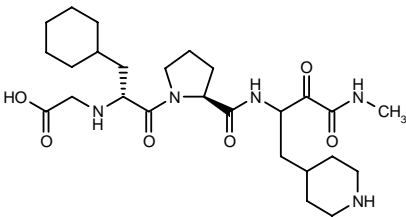
AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

255631

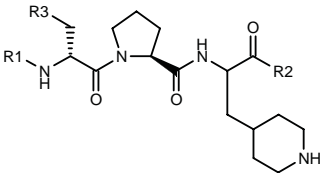
1-[Carboxymethyl-D-cyclohexylalanyl-L-prolyl-D,L-(4-piperidyl)alanyl]-N-methylformamide

3-(Carboxymethyl-D-cyclohexylalanyl-L-prolylamino)-N-methyl-2-oxo-4-(4-piperidyl)butyramide

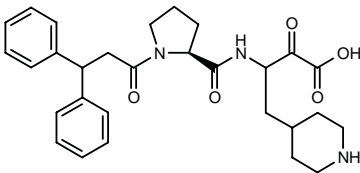


C26-H43-N5-O6; Mol wt: 521.66

ACTION – Anticoagulant and antithrombotic agent with serine protease-inhibitory activity, particularly against thrombin (IC₅₀ = 0.245 μM using human thrombin). Other representative compounds within this series of piperidine derivatives include the following:



Compound	R1	R2	R3	Formula
256501	CH2CO2H	CO2H	Ph	C ₂₅ H ₃₄ N ₄ O ₇
256503	SO2Et	CONH2	Ph	C ₂₅ H ₃₇ N ₅ O ₆ S
256504	CH2CO2H	2-thiazolyl	4-Cl-Ph	C ₂₇ H ₃₄ ClN ₅ O ₅ S
256505	CH2CO2H	2-thiazolyl	cyclooctyl	C ₂₉ H ₄₅ N ₅ O ₅ S



256502: C29-H35-N3-O5

SOURCE – Akzo Nobel.

REFERENCES

1. Adang, A.E.P. and Peters, J.A.M. (Akzo Nobel NV) *Serine protease inhibitors*. WO 9731939.

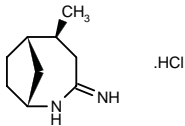
SOURCE – Searle.

REFERENCES

1. Gapud, R.E. et al. (G.D. Searle & Co.) *Hydroxyamidino derivs. useful as nitric oxide synthase inhibitors*. WO 9732844.

255720

exo-5-Methyl-2-azabicyclo[4.2.1]nonan-3-imine hydrochloride



C9-H16-N2.HCl; Mol wt: 188.70

ACTION – Nitric oxide synthase (NOS) inhibitor that preferentially inhibits the inducible isoform over the constitutive isoform (IC₅₀ = 0.133 and 82.3 μM against inducible NOS [iNOS] from mouse macrophages and human endothelial constitutive NOS [ecNOS], respectively). Potentially useful in the treatment or prevention of shock, hypotension, rheumatoid arthritis, ulcerative colitis, cerebral ischemia, insulin-dependent diabetes mellitus and cancer.

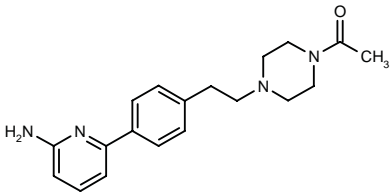
SOURCE – Ono.

REFERENCES

1. Taniguchi, N. et al. (Ono Pharm. Co., Ltd.) *Nitric oxide synthase inhibitors*. JP 97208562.

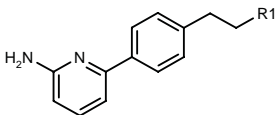
257157

6-[4-[2-(4-Acetylpiperazin-1-yl)ethyl]phenyl]pyridin-2-ylamine



C19-H24-N4-O; Mol wt: 324.42

ACTION – Nitric oxide synthase (NOS) inhibitor with potential in the treatment of septic shock, CNS disorders and inflammatory disorders. Within this series of specifically claimed 6-phenylpyridin-2-ylamine derivatives, the following are also included:



Compound	R1	Formula
258142	6-NH2-3-azabicyclo[3.1.0]hex-3-yl	C ₁₈ H ₂₂ N ₄
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258144	4-[PhCH(OH)CH2]-1-Piz	C ₂₅ H ₃₀ N ₄ O
258145	3-(4-F-PhCH2CONH)-1-pyrrolidinyl	C ₂₅ H ₂₇ FN ₄ O

SOURCE – Pfizer.

REFERENCES

1. Lowe, J.A. III and Whittle, P.J. (Pfizer, Inc.) *6-Phenylpyridyl-2-amine derivs*. WO 9736871.

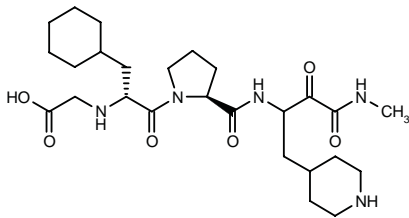
AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

255631

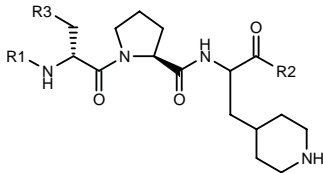
1-[Carboxymethyl-D-cyclohexylalanyl-L-prolyl-D,L-(4-piperidyl)alanyl]-N-methylformamide

3-(Carboxymethyl-D-cyclohexylalanyl-L-prolylamino)-N-methyl-2-oxo-4-(4-piperidyl)butyramide

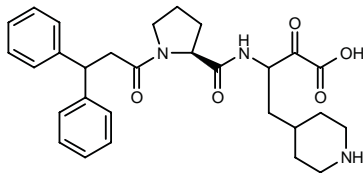


C26-H43-N5-O6; Mol wt: 521.66

ACTION – Anticoagulant and antithrombotic agent with serine protease-inhibitory activity, particularly against thrombin (IC₅₀ = 0.245 μM using human thrombin). Other representative compounds within this series of piperidine derivatives include the following:



Compound	R1	R2	R3	Formula
256501	CH2CO2H	CO2H	Ph	C ₂₅ H ₃₄ N ₄ O ₇
256503	SO2Et	CONH2	Ph	C ₂₅ H ₃₇ N ₅ O ₆ S
256504	CH2CO2H	2-thiazolyl	4-Cl-Ph	C ₂₇ H ₃₄ ClN ₅ O ₅ S
256505	CH2CO2H	2-thiazolyl	cyclooctyl	C ₂₉ H ₄₅ N ₅ O ₅ S



256502: C29-H35-N3-O5

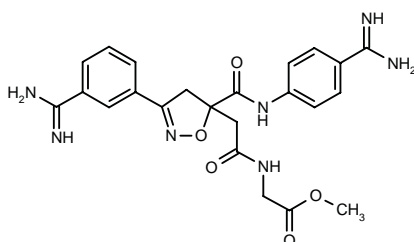
SOURCE – Akzo Nobel.

REFERENCES

1. Adang, A.E.P. and Peters, J.A.M. (Akzo Nobel NV) *Serine protease inhibitors*. WO 9731939.

256904

2-[3-(3-Amidinophenyl)-5-[*N*-(4-amidinophenyl)carbamoyl]-4,5-dihydroisoxazol-5-ylacetamido]acetic acid methyl ester



C23-H25-N7-O5; Mol wt: 479.49

ACTION – Anticoagulant, a potent factor Xa inhibitor ($K_i = 18$ nM) with selectivity over other serine proteases such as thrombin and trypsin ($K_i = 3.1$ and 0.42 μ M, respectively). Potentially useful for the treatment of both arterial and venous thrombosis.

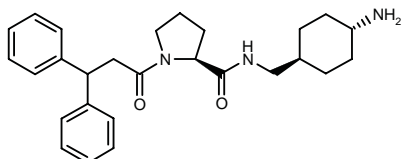
SOURCE – DuPont Merck.

REFERENCES

1. Quan, M.L. et al. (The Du Pont Merck Pharm. Co.) *Isoxazoline, isothiazoline and pyrazoline factor Xa inhibitors*. WO 9723212.
2. Quan, M.L. et al. *Bisbenzamide isoxazoline derivatives as factor Xa inhibitors*. Bioorg Med Chem Lett 1997, 7(21): 2813.

257066

N-(3,3-Diphenylpropanoyl)-L-proline *trans*-4-aminocyclohexylmethylamide



C27-H35-N3-O2; Mol wt: 433.59

ACTION – Antithrombotic agent, a potent, orally active inhibitor of thrombin ($K_i = 2$ nM) with selectivity over other human serine proteases ($K_i = 0.35$, 744, 980 and > 1000 μ M against trypsin, plasmin, factor Xa and t-PA, respectively). It displayed good oral bioavailability in dogs (58%) and a long half-life in rats ($t_{1/2} = 268$ min after 1 mg/kg i.v.) and dogs ($t_{1/2} = 175$ min after 1 mg/kg i.v. and 156 min after 5 mg/kg p.o.). *In vivo* in a rat FeCl_3 -induced carotid artery thrombosis model, the compound (10 μ g/kg/min i.v. by 120-min infusion) demonstrated good antithrombotic efficacy. The compound was selected as a second-generation lead structure for further synthetic work.

SOURCE – Merck & Co.

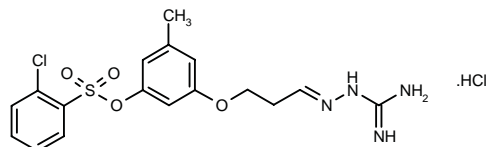
REFERENCES

1. Lumma, W.C. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. US 5510369, WO 9603374.
2. Tucker, T.J. et al. *Synthesis of a series of potent and orally bioavailable thrombin inhibitors that utilize 3,3-disubstituted propionic acid derivatives in the P3 position*. J

Med Chem 1997, 40(22): 3687.

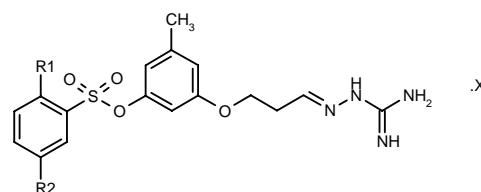
257135

N'-[3-[3-(2-Chlorophenylsulfonyloxy)-5-methylphenoxy]-propylideneamino]guanidine hydrochloride



C17-H19-Cl-N4-O4-S.HCl; Mol wt: 447.34

ACTION – Nonpeptide antithrombotic agent that acts by direct, selective inhibition of thrombin ($K_i = 13$ nM using purified human α -thrombin), but does not inhibit other proteolytic enzymes such as chymotrypsin, trypsin, elastase, urokinase, plasmin and factor Xa at concentrations of 1.6 μ M. Within this series of specifically claimed amidinohydrazones, the following are also included:



Compound	R1	R2	X	Formula
257606	CF3	H	HNO3	$\text{C}_{18}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_4\text{S} \cdot \text{HNO}_3$
257607	OMe	H	acetate	$\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_5\text{S} \cdot \text{C}_2\text{H}_4\text{O}_2$
257608	H	Br	HNO3	$\text{C}_{18}\text{H}_{21}\text{BrN}_4\text{O}_5\text{S} \cdot \text{HNO}_3$
257609	H	Me	HNO3	$\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4\text{S} \cdot \text{HNO}_3$
257610	H	Me	HNO3	$\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_4\text{S} \cdot \text{HNO}_3$
257611	OMe	Cl	HCl	$\text{C}_{18}\text{H}_{21}\text{ClN}_4\text{O}_5\text{S} \cdot \text{HCl}$
257612	H	Cl	HNO3	$\text{C}_{17}\text{H}_{19}\text{ClN}_4\text{O}_4\text{S} \cdot \text{HNO}_3$

Certain compounds within the scope of the invention are expected to inhibit trypsin and/or chymotrypsin, and are thus useful for the treatment of pancreatitis.

SOURCE – 3-Dimensional Pharm.

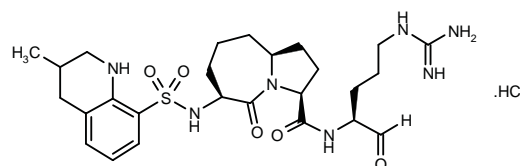
REFERENCES

1. Solli, R.M. et al. (3-Dimensional Pharm., Inc.) *Amidinohydrazones as protease inhibitors*. WO 9736580.

LR-D/009*

248991

(3*S*,6*S*,9*aS*)-*N* $^{\alpha}$ -[6-(3-Methyl-1,2,3,4-tetrahydroquinolin-8-ylsulfonamido)-5-oxoperhydropyrrolo[1,2-*a*]azepin-3-ylcarbonyl]-L-argininal hydrochloride



C26-H39-N7-O5-S.HCl; Mol wt: 598.16

ACTION – Antithrombotic agent, a potent inhibitor of human α -thrombin (IC_{50} = 0.018 μ M) with moderate to good selectivity over trypsin and plasmin (IC_{50} = 0.1 and 1.04 μ M, respectively). In a model of venous stasis thrombosis in anesthetized rats, it inhibited thrombus growth and significantly increased thrombin time. Compound was selected for further study.

SOURCES – Guidotti; Lusofarmaco; Menarini.

REFERENCES

1. Salimbeni, A. et al. (A. Menarini Ind. Farm. Riunite Srl) *Bicyclic lactam derivs. as thrombin inhibitors*. WO 9705160.

2. Salimbeni, A. et al. *Design and synthesis of conformationally restricted arginal thrombin inhibitors*. 212th ACS Natl Meet (Aug 25-29, Orlando) 1996, Abst 126.

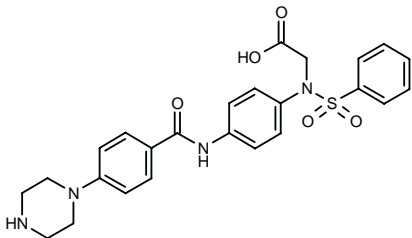
3. Salimbeni, A. et al. *Design and synthesis of conformationally constrained arginal thrombin inhibitors*. Bioorg Med Chem Lett 1997, 7(17): 2205.

*Identified compound **248991** Annu Drug Data Rep 1997, 19(7): 623.

ANTIPLATELET THERAPY

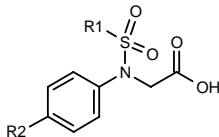
255619

N-(Phenylsulfonyl)-*N*-[4-[4-(1-piperazinyl)benzamido]-phenyl]glycine

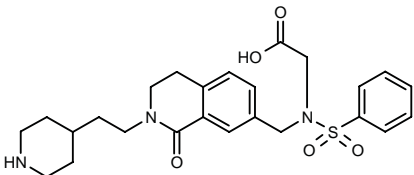


C25-H26-N4-O5-S; Mol wt: 494.56

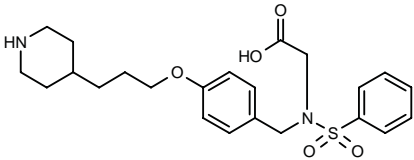
ACTION – Platelet aggregation inhibitor whose activity is mediated by fibrinogen (gpIIb/IIIa) receptor antagonism. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
256506	2-thienyl	4-(1-Piz)-PhCONH	C ₂₃ H ₂₄ N ₄ O ₅ S ₂
256507	Me	4-(1-Piz)-PhNHCO	C ₂₀ H ₂₄ N ₄ O ₅ S
256508	Ph	4-(1-Piz)-PhNHCO	C ₂₅ H ₂₆ N ₄ O ₅ S
256509	CH ₂ Ph	4-(1-Piz)-PhNHCO	C ₂₆ H ₂₈ N ₄ O ₅ S
256510	Ph	1-(4-Pyr)-4-Pip-CONH	C ₂₅ H ₂₆ N ₄ O ₅ S
256511	Ph	4-(4-Pip)-PhCONH	C ₂₆ H ₂₇ N ₃ O ₅ S
256512	Ph	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-6-yl-CONH	C ₂₆ H ₂₄ N ₄ O ₅ S



256513: C25-H31-N3-O5-S



256514: C23-H30-N2-O5-S

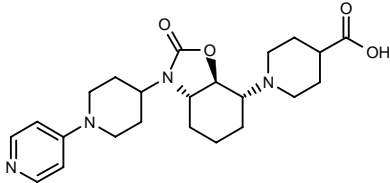
SOURCE – Merck & Co.

REFERENCES

1. Wai, J. et al. (Merck & Co., Inc.) *Fibrinogen receptor antagonists*. WO 9731910.

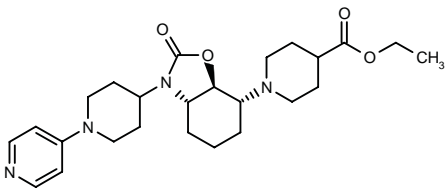
257178

(±)-(3 α ,7 β ,7 α)-1-[2-Oxo-3-[1-(4-pyridyl)piperidin-4-yl]perhydrobenzoxazol-7-yl]piperidine-4-carboxylic acid



C23-H32-N4-O4; Mol wt: 428.53

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist (IC_{50} = 25 nmol/l). Another specifically claimed compound from this series of oxazolidine derivatives is:

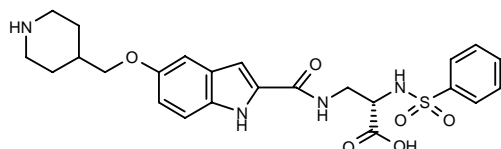


257893: C25-H36-N4-O4

SOURCE – Boehringer Mannheim.

REFERENCES

1. Tsaklakis, K. and Doerge, L. (Boehringer Mannheim GmbH) *Novel oxazolidine derivs., process for their production and medicaments containing them*. WO 9736899.

L-756568***251752****2(S)-(Phenylsulfonamido)-3-[5-(4-piperidylmethoxy)-1H-indol-2-ylcarboxamido]propionic acid****N-(Phenylsulfonyl)-3-[5-(4-piperidylmethoxy)-1H-indol-2-ylcarboxamido]-L-alanine**

C24-H28-N4-O6-S; Mol wt: 500.57

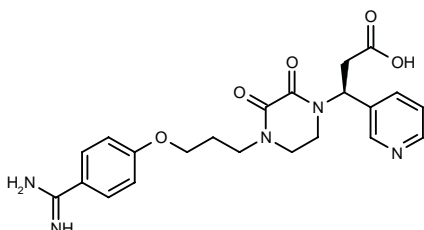
ACTION – Platelet aggregation inhibitor, a potent, orally active nonpeptide fibrinogen (gpIIb/IIIa) receptor antagonist with a long duration of action. The compound inhibited ADP-induced human platelet aggregation with an IC_{50} of 13 nM and showed moderate protein binding (66%). At a dose of 0.25 mg/kg/day p.o. in rhesus monkeys, it maintained its inhibitory effect on *ex vivo* platelet aggregation for 24 h, achieving 82-95% inhibition at trough plasma concentrations, thus indicating its suitability for once-daily dosing.

SOURCE – Merck & Co.**REFERENCES**

1. Hutchinson, J.H. and Halczenko, W. (Merck & Co., Inc.) *Fibrinogen receptor antagonist*. WO 9715568.

2. Brashear, K.M. et al. *Nonpeptide glycoprotein IIb/IIIa inhibitors: 18. Indole alpha-sulfonamide acids are potent inhibitors of platelet aggregation*. Bioorg Med Chem Lett 1997, 7(21): 2793.

*Identified compound **251752** Annu Drug Data Rep 1997, 19(8): 716.

T-250**257067****(-)-(S)-3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(3-pyridyl)propionic acid**

C22-H25-N5-O5; Mol wt: 439.47

ACTION – Platelet aggregation inhibitor, a nonpeptide fibrinogen (gpIIb/IIIa) receptor antagonist. It inhibited ADP and collagen-induced platelet aggregation and suppressed thrombus formation in animal models of thrombosis, without prolonging bleeding time. Currently in phase I clinical trials in the United Kingdom. Both oral and injectable preparations are in development.

SOURCE – Toyama.**REFERENCES**

1. Ono, S. et al. (Toyama Chem. Co., Ltd.) *Novel 2,3-diketopiperazine derivs. or salt thereof*. EP 805149, JP 96231515, WO 9616947.

2. *Start of overseas clinical study of "T-250", an anti-platelet drug (platelet-agglutination inhibitor) developed by Toyama Chemical Co., Ltd.* Toyama Chemical Co., Ltd. Press Release 1997, November 6.

3. *Toyama Chemical entered phase I of new GPIIb/IIIa antagonists (anti-platelet aggregation agent)*. Kagaku Kogyo Nippo 1997, November 7.

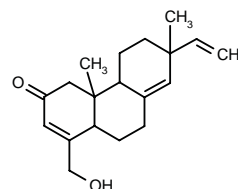
4. Toyama Chemical Co., Ltd. Company Communication 1997, November 27.

RENAL-UROLOGIC DRUGS**BENIGN PROSTATIC HYPERPLASIA THERAPY****K-4610178****255514**

ACTION – Agent for the treatment of benign prostatic hypertrophy, an inhibitor of 5α -reductase (IC_{50} = 6.4 μ M against rat prostate enzyme) isolated from the culture of *Thielavia subthemophila* Mouchacca SANK 31281 (FERM BP-5213).

SOURCE – Sankyo.**REFERENCES**

1. Sugano, M. et al. (Sankyo Co., Ltd.) *Novel cpd. k4610178*. JP 97221493.

K-4610422**255508****1-(Hydroxymethyl)-4a,7-dimethyl-7-vinyl-3,4,4a,4b,5,6,7,9,10,10a-decahydrophenanthren-3-one**

C19-H26-O2; Mol wt: 286.41

ACTION – Agent for the treatment of benign prostatic hypertrophy isolated from cultures of *Streptosporangium* sp. SANK 62195 (FERM BP-5200), an inhibitor of 5α -reductase (IC_{50} = 7.8 μ g/ml against rat prostate enzyme).

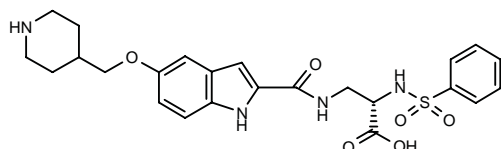
SOURCE – Sankyo.**REFERENCES**

1. Sugano, M. et al. (Sankyo Co., Ltd.) *Novel cpd. k4610422*. JP 97221448.

L-756568***251752**

2(S)-(Phenylsulfonamido)-3-[5-(4-piperidylmethoxy)-1H-indol-2-ylcarboxamido]propionic acid

N-(Phenylsulfonyl)-3-[5-(4-piperidylmethoxy)-1H-indol-2-ylcarboxamido]-L-alanine



C24-H28-N4-O6-S; Mol wt: 500.57

ACTION – Platelet aggregation inhibitor, a potent, orally active nonpeptide fibrinogen (gpIIb/IIIa) receptor antagonist with a long duration of action. The compound inhibited ADP-induced human platelet aggregation with an IC_{50} of 13 nM and showed moderate protein binding (66%). At a dose of 0.25 mg/kg/day p.o. in rhesus monkeys, it maintained its inhibitory effect on *ex vivo* platelet aggregation for 24 h, achieving 82-95% inhibition at trough plasma concentrations, thus indicating its suitability for once-daily dosing.

SOURCE – Merck & Co.**REFERENCES**

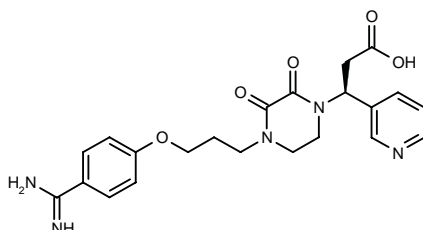
1. Hutchinson, J.H. and Halczenko, W. (Merck & Co., Inc.) *Fibrinogen receptor antagonist*. WO 9715568.

2. Brashear, K.M. et al. *Nonpeptide glycoprotein IIb/IIIa inhibitors: 18. Indole alpha-sulfonamide acids are potent inhibitors of platelet aggregation*. Bioorg Med Chem Lett 1997, 7(21): 2793.

*Identified compound **251752** Annu Drug Data Rep 1997, 19(8): 716.

T-250**257067**

(–)-(S)-3-[4-[3-(4-Amidinophenoxy)propyl]-2,3-dioxopiperazin-1-yl]-3-(3-pyridyl)propionic acid



C22-H25-N5-O5; Mol wt: 439.47

ACTION – Platelet aggregation inhibitor, a nonpeptide fibrinogen (gpIIb/IIIa) receptor antagonist. It inhibited ADP and collagen-induced platelet aggregation and suppressed thrombus formation in animal models of thrombosis, without prolonging bleeding time. Currently in phase I clinical trials in the United Kingdom. Both oral and injectable preparations are in development.

SOURCE – Toyama.**REFERENCES**

1. Ono, S. et al. (Toyama Chem. Co., Ltd.) *Novel 2,3-diketopiperazine derivs. or salt thereof*. EP 805149, JP 96231515, WO 9616947.

2. *Start of overseas clinical study of "T-250", an anti-platelet drug (platelet-agglutination inhibitor) developed by Toyama Chemical Co., Ltd.* Toyama Chemical Co., Ltd. Press Release 1997, November 6.

3. *Toyama Chemical entered phase I of new GPIIb/IIIa antagonists (anti-platelet aggregation agent)*. Kagaku Kogyo Nippo 1997, November 7.

4. Toyama Chemical Co., Ltd. Company Communication 1997, November 27.

RENAL-UROLOGIC DRUGS**BENIGN PROSTATIC
HYPERPLASIA THERAPY****K-4610178****255514**

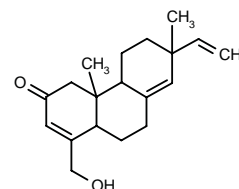
ACTION – Agent for the treatment of benign prostatic hypertrophy, an inhibitor of 5α -reductase (IC_{50} = 6.4 μ M against rat prostate enzyme) isolated from the culture of *Thielavia subthemophila* Mouchacca SANK 31281 (FERM BP-5213).

SOURCE – Sankyo.**REFERENCES**

1. Sugano, M. et al. (Sankyo Co., Ltd.) *Novel cpd. k4610178*. JP 97221493.

K-4610422**255508**

1-(Hydroxymethyl)-4a,7-dimethyl-7-vinyl-3,4,4a,4b,5,6,7,9,10,10a-decahydrophenanthren-3-one



C19-H26-O2; Mol wt: 286.41

ACTION – Agent for the treatment of benign prostatic hypertrophy isolated from cultures of *Streptosporangium* sp. SANK 62195 (FERM BP-5200), an inhibitor of 5α -reductase (IC_{50} = 7.8 μ g/ml against rat prostate enzyme).

SOURCE – Sankyo.**REFERENCES**

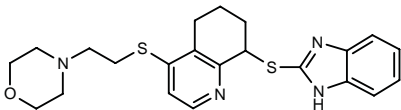
1. Sugano, M. et al. (Sankyo Co., Ltd.) *Novel cpd. k4610422*. JP 97221448.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

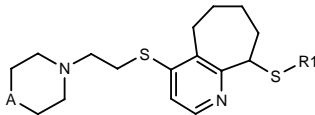
255074

8-(Benzimidazol-2-ylsulfany)-4-[2-(4-morpholinyl)ethyl-sulfany]-5,6,7,8-tetrahydroquinoline



C22-H26-N4-O-S2; Mol wt: 426.59

ACTION – Antiulcer agent with potent and selective activity against *Helicobacter pylori* (MIC = 0.29 µg/ml; MIC values against a broad range of Gram-positive and Gram-negative bacteria > 512 µg/ml). Other compounds from this series of cycloalkanopyridine derivatives include the following:



Compound	R1	A	Formula
257827	2-benzimidazolyl	O	C ₂₃ H ₂₈ N ₄ OS ₂
257828	purin-6-yl	CH ₂	C ₂₂ H ₂₈ N ₆ S ₂
257829	5-Me-1,3,4-thiadiazol-2-yl	O	C ₁₉ H ₂₈ N ₄ OS ₃
257830	purin-6-yl	O	C ₂₁ H ₂₈ N ₆ OS ₂
257831	5-MeO-2-benzimidazolyl	O	C ₂₄ H ₃₀ N ₄ O ₂ S ₂
257832	pyrazolo[3,4-d]pyrimidin-4-yl	O	C ₂₁ H ₂₆ N ₆ OS ₂

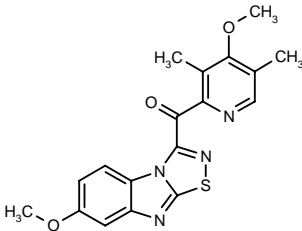
SOURCE – Toa Eiyo.

REFERENCES

1. Takayanagi, K. et al. (Toa Eiyo, Ltd.) *Cycloalkanopyridine derivs., process for producing the same, and peptic ulcer remedy comprising the same.* WO 9730988.

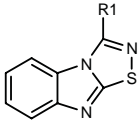
255394

1-(4-Methoxy-3,5-dimethyl-2-pyridyl)-1-(7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazol-3-yl)methanone



C18-H16-N4-O3-S; Mol wt: 368.41

ACTION – Antiulcer agent, an inhibitor of H⁺/K⁺-ATPase proven to significantly inhibit meal-stimulated gastric acid secretion in rats at 300 µmol/kg by oral gavage and histamine-stimulated gastric acid secretion in rats at doses of 3-300 µg/kg by oral gavage. Other specifically claimed thiadiazole compounds include the following:



Compound	R1	Formula
255920	4-Me-1-Piz	C ₁₃ H ₁₅ N ₅ S
255921	4-morpholinyl	C ₁₂ H ₁₂ N ₄ OS
255922	4-Ac-1-Piz	C ₁₄ H ₁₅ N ₅ OS
256125	1-pyrrolidinyl	C ₁₂ H ₁₂ N ₄ S
256126	4-Me-PhSO ₂	C ₁₅ H ₁₁ N ₃ O ₂ S ₂

SOURCE – Apotex.

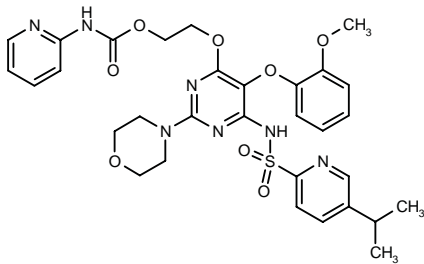
REFERENCES

1. Karimian, K. et al. (Apotex, Inc.) *Thiadiazole cpds. useful as proton pump inhibitors.* US 5677302, WO 9731923.

RO-48-5695*

237868

N-(2-Pyridyl)carbamic acid 2-[6-(5-isopropylpyridin-2-ylsulfonamido)-5-(2-methoxyphenoxy)-2-(4-morpholinyl)pyrimidin-4-yloxy]ethyl ester



C31-H35-N7-O8-S; Mol wt: 665.72

ACTION – Potent, orally active mixed endothelin receptor antagonist with high affinity for both ET_A (IC₅₀ = 0.3 and 0.7 nM against recombinant human receptors expressed in Sf9 and CHO cells, respectively) and ET_B receptors (IC₅₀ = 5 nM in human placenta membranes) and much improved potency over bosentan. It demonstrated functional antagonist activity against ET-1-induced constriction of rat aortic rings (ET_A) and sarafotoxin S6c-induced constriction of rat tracheal rings (ET_B) (pA₂ = 9.3 and 7.6, respectively) and ET-1-induced intracellular calcium mobilization in HEK-294 cells cotransfected with human recombinant ET_A or ET_B receptors (IC₅₀ = 0.9 and 6 nM, respectively). The sodium salt showed good oral bioavailability (40-60%) in rats and dogs. In mice, it dose-dependently (0.1-10 mg/kg p.o.) reduced indomethacin-induced gastric mucosal damage and ulceration and reduced myeloperoxidase activity, indicating reduction of neutrophil infiltration and prevention of inflammation; it did not inhibit gastric secretion and its activity is suggested to involve inhibition of endothelin-induced vasoconstriction.

SOURCE – Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *Sulfonamides*. CA 2162630, EP 713875, JP 96208625.
2. Huang, J.Q. et al. *The preventive effect of a new endothelin receptor antagonist (ETRA) (Ro 48-5695) on indomethacin-induced acute gastropathy*. Gastroenterology 1997, 112(4, Suppl.): A153.
3. Neidhart, W. et al. *Discovery of RO 48-5695: A potent mixed endothelin receptor antagonist optimized from bosentan*. Bioorg Med Chem Lett 1997, 7(17): 2223.
4. Russell, A.L. and Hardie, F. *Identification of the involvement of human liver CYP2D6 and CYP2C19 in the metabolism of Ro-48-5695*. 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 197.

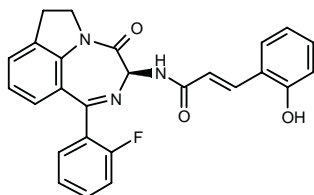
*Identified compound **237868** (see **237285**) Annu Drug Data Rep 1996, 18(8): 707.

TREATMENT OF PANCREATIC DISORDERS

FR-127519

255380

N-[1-(2-Fluorophenyl)-4-oxo-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-3(*S*)-yl]-3-(2-hydroxyphenyl)-2(*E*)-propenamide



C26-H20-F-N3-O3; Mol wt: 441.46

M.p. 178-92 °C (*decomp.*).

ACTION – A potent and orally active cholecystokinin CCK_A receptor antagonist shown to inhibit [¹²⁵I]-CCK-8 binding to rat pancreatic membranes with an IC₅₀ of 0.52 nM, and to concentration-dependently antagonize CCK actions in rat nodose ganglion. *In vivo* it suppressed the CCK-8-induced inhibition of the emptying of a charcoal meal in mice (ED₅₀ = 0.017 mg/kg p.o.). Potentially useful for the treatment of chronic pancreatitis.

SOURCE – Fujisawa.

REFERENCES

1. Sato, Y. et al. (Fujisawa Pharm. Co., Ltd.) *Tricyclic cpds., processes for their preparation and pharmaceutical compns. comprising them*. EP 360079, JP 90111774, JP 95041480, JP 95048373, US 4981847, US 5155101, US 5401737, US 5461048.
2. Beart, P.M. et al. *Analyses of FR127519 and KSG-504 as cholecystokinin_A receptor antagonists in the rat isolated nodose ganglion*. Pharmacol Rev Commun 1997, 9(1-2): 27.
3. Satoh, Y. et al. *Studies on a novel, potent and orally effective cholecystokinin A antagonist, FK-480. Synthesis and structure-activity relationships of FK-480 and related compounds*. Chem Pharm Bull 1994, 42(10): 2071.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

255090

[[*N*^ε-(17-Carboxyheptadecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

29B-[*N*^ε-(17-Carboxyheptadecanoyl)-L-lysine]-30B-de-L-alanineinsulin (human)

ACTION – Antidiabetic agent, an insulin analog derived from naturally occurring insulins, characterized by its solubility at physiological pH and long disappearance half-life from the injection site after s.c. injection (17.1 h). Other exemplified insulin derivatives include the following:

[[*N*^ε-(13-Carboxytridecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

256306

[[*N*^ε-(15-Carboxypentadecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

256307

[[*N*^ε-(19-Carboxynonadecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

256308

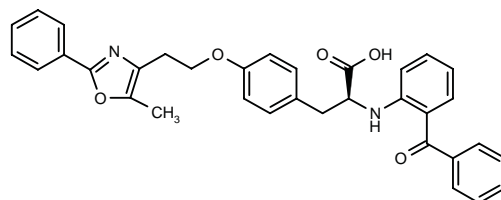
SOURCE – Novo Nordisk.

REFERENCES

1. Schäffer, L. and Balschmidt, P. (Novo Nordisk A/S) *Insulin derivs. and their use*. WO 9731022.

255618

2(*S*)-(2-Benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]propionic acid



C34-H30-N2-O5; Mol wt: 546.62

SOURCE – Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *Sulfonamides*. CA 2162630, EP 713875, JP 96208625.
2. Huang, J.Q. et al. *The preventive effect of a new endothelin receptor antagonist (ETRA) (Ro 48-5695) on indomethacin-induced acute gastropathy*. Gastroenterology 1997, 112(4, Suppl.): A153.
3. Neidhart, W. et al. *Discovery of RO 48-5695: A potent mixed endothelin receptor antagonist optimized from bosentan*. Bioorg Med Chem Lett 1997, 7(17): 2223.
4. Russell, A.L. and Hardie, F. *Identification of the involvement of human liver CYP2D6 and CYP2C19 in the metabolism of Ro-48-5695*. 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 197.

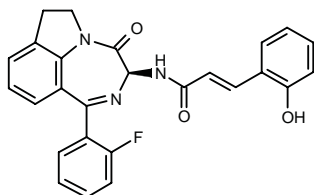
*Identified compound **237868** (see **237285**) Annu Drug Data Rep 1996, 18(8): 707.

TREATMENT OF PANCREATIC DISORDERS

FR-127519

255380

N-[1-(2-Fluorophenyl)-4-oxo-3,4,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-3(*S*)-yl]-3-(2-hydroxyphenyl)-2(*E*)-propanamide



C26-H20-F-N3-O3; Mol wt: 441.46

M.p. 178-92 °C (*decomp.*).

ACTION – A potent and orally active cholecystokinin CCK_A receptor antagonist shown to inhibit [¹²⁵I]-CCK-8 binding to rat pancreatic membranes with an IC₅₀ of 0.52 nM, and to concentration-dependently antagonize CCK actions in rat nodose ganglion. *In vivo* it suppressed the CCK-8-induced inhibition of the emptying of a charcoal meal in mice (ED₅₀ = 0.017 mg/kg p.o.). Potentially useful for the treatment of chronic pancreatitis.

SOURCE – Fujisawa.

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1. Sato, Y. et al. (Fujisawa Pharm. Co., Ltd.) *Tricyclic cpds., processes for their preparation and pharmaceutical compns. comprising them*. EP 360079, JP 90111774, JP 95041480, JP 95048373, US 4981847, US 5155101, US 5401737, US 5461048.
2. Beart, P.M. et al. *Analyses of FR127519 and KSG-504 as cholecystokinin_A receptor antagonists in the rat isolated nodose ganglion*. Pharmacol Rev Commun 1997, 9(1-2): 27.
3. Satoh, Y. et al. *Studies on a novel, potent and orally effective cholecystokinin A antagonist, FK-480. Synthesis and structure-activity relationships of FK-480 and related compounds*. Chem Pharm Bull 1994, 42(10): 2071.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

255090

[[*N*^ε-(17-Carboxyheptadecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

29B-[*N*^ε-(17-Carboxyheptadecanoyl)-L-lysine]-30B-de-L-alanineinsulin (human)

ACTION – Antidiabetic agent, an insulin analog derived from naturally occurring insulins, characterized by its solubility at physiological pH and long disappearance half-life from the injection site after s.c. injection (17.1 h). Other exemplified insulin derivatives include the following:

[[*N*^ε-(13-Carboxytridecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

256306

[[*N*^ε-(15-Carboxypentadecanoyl)]Lys(B29),des-Ala(B30)]-insulin (human)

256307

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256308

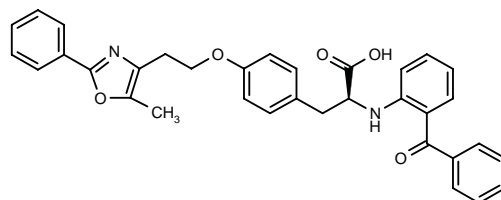
SOURCE – Novo Nordisk.

REFERENCES

1. Schäffer, L. and Balschmidt, P. (Novo Nordisk A/S) *Insulin derivs. and their use*. WO 9731022.

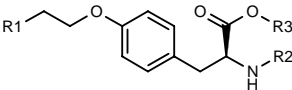
255618

2(*S*)-(2-Benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]propionic acid

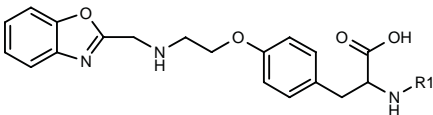


C34-H30-N2-O5; Mol wt: 546.62

ACTION – Peroxisome proliferator-activated receptor (PPAR)- γ agonist ($K_i = 20\text{ nM}$; $EC_{50} = 0.2\text{ nM}$ in a PPAR- γ cotransfection assay) with good blood glucose-lowering activity (70% decrease in glucose levels in db/db mice at 5 mg/kg p.o. b.i.d. for 14 days). Potentially useful for the treatment or prevention of hyperglycemia, dyslipidemia, type II diabetes, type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, obesity, anorexia, bulimia and cardiovascular diseases such as atherosclerosis. Within this series of specifically claimed substituted 4-hydroxyphenylpropionic acid derivatives, the following are also included:



Compound	R1	R2	R3	Formula
256566	5-Me-2-Ph-4-oxazolyl	2-(CO2Me)-Ph	H	C ₂₉ H ₂₈ N ₂ O ₆
256567	2-benzoxazolyl-CH2NH	2-(PhCO)-Ph	H	C ₃₂ H ₂₉ N ₃ O ₅
256570	5-Me-2-(4-Me-1-Piz)-4-thiazolyl	2-CO2H-Ph	Me	C ₂₈ H ₃₄ N ₄ O ₅ S



256568	2-(cyclohexyl-CO)-Ph	C ₃₂ H ₃₅ N ₃ O ₅
256569	2-(PhCO)-3-thienyl	C ₃₀ H ₂₇ N ₃ O ₅ S

SOURCE – Glaxo Wellcome.

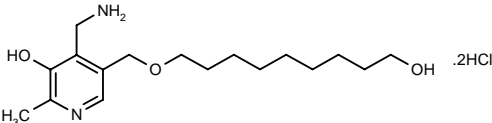
REFERENCES

1. Willson, T.M. et al. (Glaxo Group, Ltd.) *Substd. 4-hydroxy-phenylalcanoic acid derivs. with agonist activity to PPAR- γ* . WO 9731907.

TREATMENT OF DIABETIC COMPLICATIONS

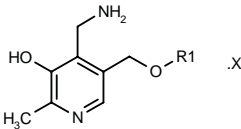
255510

4-(Aminomethyl)-3-hydroxy-5-(9-hydroxynonyloxymethyl)-2-methylpyridine dihydrochloride



C17-H30-N2-O3.2HCl; Mol wt: 383.36

ACTION – Agent for the treatment of diabetic complications and aging-associated disorders, an inhibitor of the Maillard reaction. A representative compound from a series of 4-aminomethyl-3-hydroxypyridine derivatives, wherein the following are also included:



Compound	R1	.X	Formula
257328	4-MeO-PhCH2		C ₁₆ H ₂₀ N ₂ O ₃
257329	cyclohexyl-CH2		C ₁₅ H ₂₄ N ₂ O ₂
257330	6-OH-2,5,7,8-(Me)4-3,4-dihydro-2H-benzopyran-2-yl-CH2CH2	2HCl	C ₂₃ H ₃₂ N ₂ O ₄ .2HCl
257331	C7H15		C ₁₅ H ₂₆ N ₂ O ₂

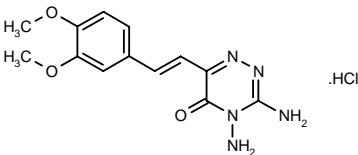
SOURCE – Kissei.

REFERENCES

1. Ikube, R. et al. (Kissei Pharm. Co., Ltd.) *3-Hydroxy-4-aminomethylpyridine derivs. and inhibitors to Maillard reaction, including this derivs.* JP 97221473.

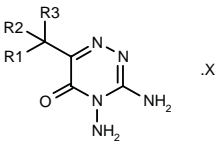
256202

3,4-Diamino-6-[2(E)-(3,4-dimethoxyphenyl)vinyl]-1,2,4-triazin-5(4H)-one hydrochloride



C13-H15-N5-O3.HCl; Mol wt: 325.75

ACTION – Agent for the treatment of diabetic complications and age-related diseases that acts by inhibiting the formation of advanced glycosylation endproducts (AGEs) and protein crosslinks. Activity of the compound was evaluated by measuring its ability to inhibit the crosslinking of N-acetyl-glycyl-lysine methyl ester in the presence of ribose ($IC_{50} = 0.35\text{ mM}$). Compound is also claimed for use in preventing the staining of teeth. Other compounds from this series of 1,2,4-triazine derivatives include the following:



Compound	R1	R2	R3	.X	Formula
257563	H	2-NO2-Ph	H	HCl	C ₁₀ H ₁₀ N ₆ O ₃ .HCl
257564	H	CH2CO2H	H	HCl	C ₈ H ₁₉ N ₅ O ₃ .HCl
257565	H	CH2CO2Et	H	HCl	C ₉ H ₁₃ N ₅ O ₃ .HCl
257566	H	C6H13	CO2Et	HCl	C ₁₃ H ₂₃ N ₅ O ₃ .HCl
257567		-O-	NHNH2		C ₄ H ₇ N ₇ O ₂
257569	Me	CH2OH	Me		C ₇ H ₁₃ N ₅ O ₂

SOURCE – Alteon.

REFERENCES

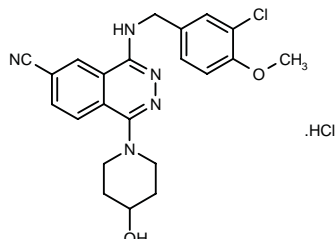
1. Wagle, D.R. et al. (Alteon, Inc.) *1,2,4-Triazine derivs. for the inhibition of protein glycosylation.* WO 9735849.

TREATMENT OF MALE REPRODUCTIVE DYSFUNCTION

E-4010

257647

4-(3-Chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)phthalazine-6-carbonitrile hydrochloride



C₂₂H₂₂Cl-N₅O₂.HCl; Mol wt: 460.36

ACTION – Potent, selective and structurally distinct inhibitor of phosphodiesterase type V (PDE V; IC₅₀ = 0.56 nM), a representative compound from a series of phthalazine derivatives.

SOURCE – Eisai.

REFERENCES

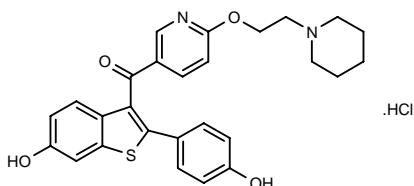
1. Watanabe, N. et al. (Eisai Co., Ltd.) *Fused pyridazine cpd.* EP 722936, JP 96225541, WO 9605176.

2. Watanabe, N. et al. *Phthalazine derivatives: Novel potent and selective PDE V inhibitors.* 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-33.

TREATMENT OF GYNECOLOGICAL DISORDERS

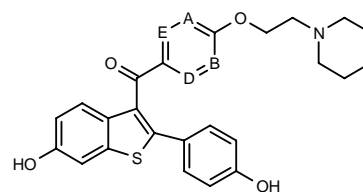
256340

1-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-1-[6-[2-(1-piperidinyloxy)pyridin-3-yl]methanone hydrochloride



C₂₇H₂₆N₂O₄.S.HCl; Mol wt: 511.03

ACTION – Agent for the treatment of postmenopausal syndrome including osteoporosis, hyperlipidemia, breast and uterine cancer, and also for the treatment of uterine fibroid disease, endometriosis and aortic smooth muscle proliferation. At a dose of 0.1 mg/kg/day p.o. the compound produced a significant decrease in serum cholesterol but a substantially lower increase in uterine weight as compared to 17 α -ethinylestradiol in ovariectomized rats. It also prevented bone loss in a dose-dependent manner in ovariectomized rats, and inhibited the proliferation of breast adenocarcinoma MCF-7 cells (IC₅₀ = 10 nM). Other specifically claimed heterocyclic substituted benzothio-phenes include the following:



Compound	A	B	D	E	Formula
257103	N	N	CH	CH	C ₂₆ H ₂₅ N ₃ O ₄ S
257104	CH	CH	N	N	C ₂₆ H ₂₅ N ₃ O ₄ S
257105	CH	N	CH	N	C ₂₆ H ₂₅ N ₃ O ₄ S
257106	N	CH	CH	N	C ₂₆ H ₂₅ N ₃ O ₄ S
257107	CH	CH	CH	N	C ₂₇ H ₂₆ N ₂ O ₄ S

SOURCE – Lilly.

REFERENCES

1. Cullinan, G.J. and Fahey, K.J. (Eli Lilly & Co.) *Heterocyclic subst. benzothio-phenes and pharmaceutical compsns.* EP 801066, US 5688796.

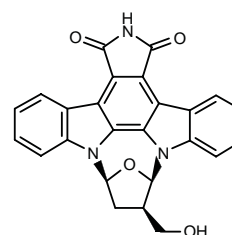
DERMATOLOGIC DRUGS

ANTIPSORIATICS

SCH-47112*

189740

(9*R*,10*R*,12*S*)-9,12-Epoxy-10-(hydroxymethyl)-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*][1,6]benzodiazocine-1,3-dione



C₂₅H₁₇N₃O₄; Mol wt: 423.43

ACTION – Protein kinase C (PKC) inhibitor derived from staurosporine that interacts with the catalytic domain of PKC. The compound applied to the dorsum at 100 nmol inhibited TPA-induced epidermal, upper dermal and deep dermal inflammation in mice by 71, 45 and 22%, respectively, and at 400 nmol it inhibited TPA-induced epidermal hyperplasia by 38%. Like staurosporine, it inhibited TPA-induced transglutaminase I protein accumulation in human keratinocytes and inhibited keratinocyte growth at 10-100 nM. Potentially useful in the treatment of psoriasis.

SOURCE – Schering-Plough.

REFERENCES

1. McCombie, S.W. et al. (Schering Corp.) *Anti-tumor and anti-psoriatic agents.* EP 508792, EP 508012, JP 94503837, WO 9218507.

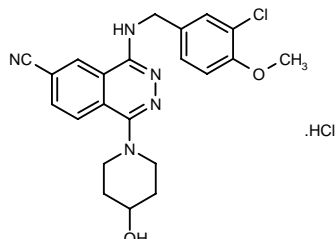
2. McCombie, S.W. et al. *Indolocarbazoles. 1. Total synthesis and protein kinase inhibiting characteristics of compounds related to K-252c.* Bioorg Med Chem Lett 1993, 3(8): 1537.

TREATMENT OF MALE REPRODUCTIVE DYSFUNCTION

E-4010

257647

4-(3-Chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)phthalazine-6-carbonitrile hydrochloride



C₂₂H₂₂ClN₅O₂.HCl; Mol wt: 460.36

ACTION – Potent, selective and structurally distinct inhibitor of phosphodiesterase type V (PDE V; IC₅₀ = 0.56 nM), a representative compound from a series of phthalazine derivatives.

SOURCE – Eisai.

REFERENCES

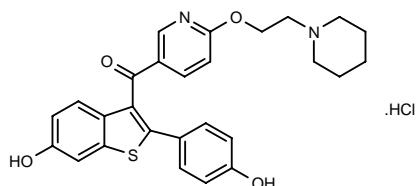
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TREATMENT OF GYNECOLOGICAL DISORDERS

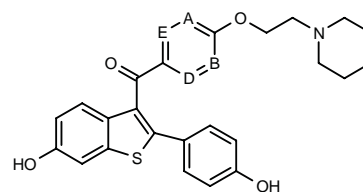
256340

1-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-1-[6-[2-(1-piperidinyloxy)pyridin-3-yl]methanone hydrochloride



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257105	CH	N	CH	N	C ₂₆ H ₂₅ N ₃ O ₄ S
257106	N	CH	CH	N	C ₂₆ H ₂₅ N ₃ O ₄ S
257107	CH	CH	CH	N	C ₂₇ H ₂₆ N ₂ O ₄ S

SOURCE – Lilly.

REFERENCES

1. Cullinan, G.J. and Fahey, K.J. (Eli Lilly & Co.) *Heterocyclic subst. benzothio-phenes and pharmaceutical compsns.* EP 801066, US 5688796.

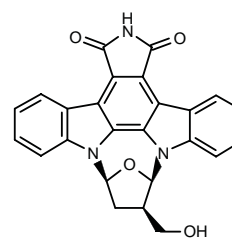
DERMATOLOGIC DRUGS

ANTIPSORIATICS

SCH-47112*

189740

(9*R*,10*R*,12*S*)-9,12-Epoxy-10-(hydroxymethyl)-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*][1,6]benzodiazocine-1,3-dione



C₂₅H₁₇N₃O₄; Mol wt: 423.43

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SOURCE – Schering-Plough.

REFERENCES

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2. McCombie, S.W. et al. *Indolocarbazoles. 1. Total synthesis and protein kinase inhibiting characteristics of compounds related to K-252c.* Bioorg Med Chem Lett 1993, 3(8): 1537.

3. Reynolds, N.J. et al. *SCH 47112, a novel staurosporine derivative, inhibits 12-O-tetradecanoylphorbol-13-acetate-induced inflammation and epidermal hyperplasia in hairless mouse skin.* Arch Dermatol Res 1997, 289(9): 540.

4. Reynolds, N.J. et al. *Inhibition of phorbol ester-induced cutaneous inflammation and epidermal hyperplasia in hairless mouse skin by SCH 47112, a novel staurosporine derivative.* Brit J Dermatol 1996, 134(3): 586.

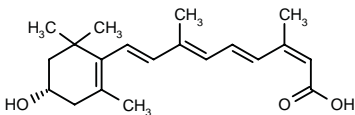
5. Reynolds, N.J. et al. *SCH 47112, a novel staurosporine derivative, inhibits 12-O-tetradecanoylphorbol-13-acetate-induced inflammation and epidermal hyperplasia in hairless mouse skin.* J Invest Dermatol 1996, 106(4): Abst 633.

*Identified compound **189740** Annu Drug Data Rep 1993, 15(4): 385.

ACNE THERAPY

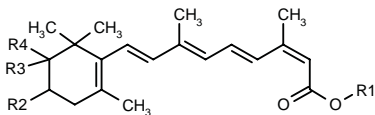
256344

(2Z,4E,6E,8E)-9-[4(R)-Hydroxy-2,6,6-trimethyl-1-cyclohexenyl]-3,7-dimethylnona-2,4,6,8-tetraenoic acid

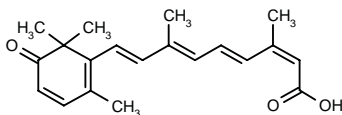


C20-H28-O3; Mol wt: 316.44

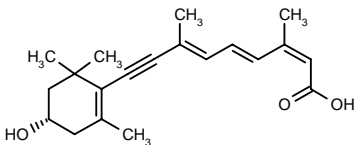
ACTION – Retinoid for the treatment or prevention of skin-related disorders such as acne, psoriasis and cancerous and precancerous conditions. Activity was demonstrated *in vivo* in a minipig model, where administration of 10 mg/kg p.o. of the compound for 8 weeks produced a significant reduction in sebaceous glands, which was already visible after 3-4 weeks of treatment; no adverse effects were reported at doses up to 50 mg/kg. Compound was also shown to be devoid of the teratogenic side effects associated with other retinoid products such as isotretinoin or tretinoin (IC₅₀ > 1000 nM vs. 200 and 80 nM, respectively, in the limb bud cell culture assay). Other specifically claimed retinoids include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
257125	Et	OH	H	H	R	C ₂₂ H ₃₂ O ₃
257126	H	OH	H	H	S	C ₂₀ H ₂₈ O ₃
257127	H	H	OH	H		C ₂₀ H ₂₈ O ₃
257129	H	H	-O-			C ₂₀ H ₂₆ O ₃



257128: C20-H24-O3



257130: C20-H26-O3

SOURCE – Roche.

REFERENCES

1. Klaus, M. and Mohr, P. (F. Hoffmann-La Roche AG) *Retinoids*. EP 802181.

WOUND-HEALING AGENTS

H1305

254178

ACTION – Novel chemokine that displays chemotactic activity. Potentially useful for the treatment of wounds and for inhibiting viral replication, including the replication of HIV. Antibodies to H1305 protein may be useful for the treatment of certain tumors.

SOURCE – Genetics Inst.

REFERENCES

1. Racie, L.A. et al. (Genetics Inst., Inc.) *β-Chemokine, H1305 (MCP-2)*. WO 9725427.

KGF_(des1-23)

255390

Seryl-tyrosyl-aspartyl-tyrosyl-methionyl-glutamyl-glycyl-glycyl-aspartyl-isoleucyl-arginyl-valyl-arginyl-arginyl-leucyl-phenylalanyl-cysteinyl-arginyl-threonyl-glutamyl-tryptophanyl-tyrosyl-leucyl-arginyl-isoleucyl-aspartyl-lysyl-arginyl-glycyl-lysyl-valyl-lysyl-glycyl-threonyl-glutamyl-glutamyl-methionyl-lysyl-asparaginyl-asparaginyl-tyrosyl-asparaginyl-isoleucyl-methionyl-glutamyl-isoleucyl-arginyl-threonyl-valyl-alanyl-valyl-glycyl-isoleucyl-valyl-alanyl-isoleucyl-lysyl-glycyl-valyl-glutamyl-seryl-glutamyl-phenylalanyl-tyrosyl-leucyl-alanyl-methionyl-asparaginyl-lysyl-glutamyl-glycyl-lysyl-leucyl-tyrosyl-alanyl-lysyl-lysyl-glutamyl-cysteinyl-asparaginyl-glutamyl-aspartyl-cysteinyl-asparaginyl-phenylalanyl-lysyl-glutamyl-leucyl-isoleucyl-leucyl-glutamyl-asparaginyl-histidyl-tyrosyl-asparaginyl-threonyl-tyrosyl-alanyl-seryl-alanyl-lysyl-tryptophanyl-threonyl-histidyl-asparaginyl-glycyl-glycyl-glutamyl-methionyl-phenylalanyl-valyl-alanyl-leucyl-asparaginyl-glutamyl-lysyl-glycyl-isoleucyl-prolyl-valyl-arginyl-glycyl-lysyl-lysyl-threonyl-lysyl-lysyl-glutamyl-glutamyl-lysyl-threonyl-alanyl-histidyl-phenylalanyl-leucyl-prolyl-methionyl-alanyl-isoleucyl-threonine

C724-H1147-N203-O206-S9; Mol wt: 16279.80

ACTION – Agent for promoting wound healing and for the treatment of hyperproliferative diseases of the epidermis, a keratinocyte growth factor (KGF) fragment lacking the first 23 *N*-terminal amino acids of mature recombinant KGF, reported to exhibit a 7-10-fold increase in mitogenic activity, as demonstrated in Balb/C-Mk cells (ED₅₀ approx. 24 pg/ml vs. approx. 250 pg/ml for mature rKGF), and reduced cytotoxicity compared to the mature full-length KGF.

SOURCE – Chiron.

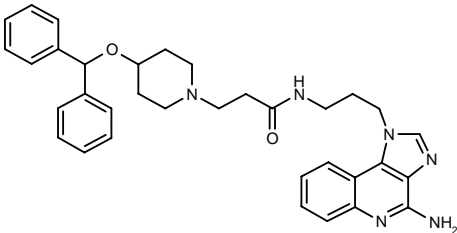
REFERENCES

1. Gospodarowicz, D.J. and Masiarz, F.R. (Chiron Corp.) *Truncated keratinocyte growth factor (KGF) having increased biological activity*. US 5677278.

MISCELLANEOUS DERMATOLOGIC DRUGS

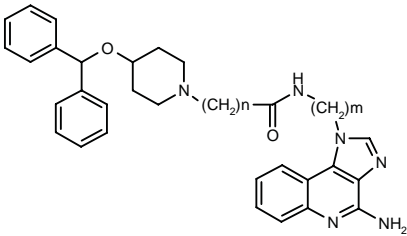
255496

N-[3-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]-3-[4-(diphenylmethoxy)piperidin-1-yl]propionamide



C34-H38-N6-O2; Mol wt: 562.71

ACTION – Agent for the treatment of allergic disorders such as atopic dermatitis, shown to possess antihistaminic activity (IC₅₀ = 0.34 μM for inhibition of histamine-induced contractions of isolated guinea pig trachea) and to inhibit eosinophil infiltration into the skin of *Dermatophagoides pteronyssinus* extract-sensitized mice (41.46% inhibition when applied topically as a 2% ointment). Compound was also shown to inhibit ovalbumin-induced ear edema in mice following i.p. or p.o. administration. Within this series of amido derivatives, the following are also included:



Compound	m	n	Formula
256869	4	2	C ₃₅ H ₄₀ N ₆ O ₂
256871	3	3	C ₃₅ H ₄₀ N ₆ O ₂
256872	3	4	C ₃₆ H ₄₂ N ₆ O ₂
256873	3	5	C ₃₇ H ₄₄ N ₆ O ₂

SOURCE – Terumo.

REFERENCES

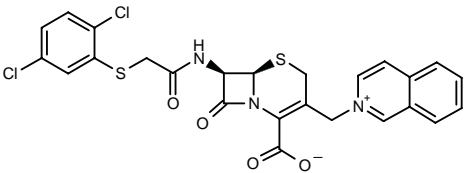
1. Naniwa, R. et al. (Terumo Corp.) *Amido derivs., medicine including the same and their synthetic intermediates*. JP 97208584.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

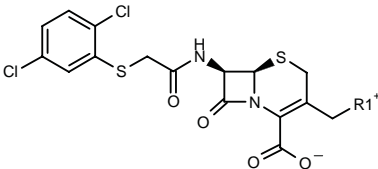
256890

(6*R*,7*R*)-7-[2-(2,5-Dichlorophenylsulfanyl)acetamido]-3-(isoquinolinium-2-ylmethyl)-3-cephem-4-carboxylic acid inner salt



C25-H19-Cl2-N3-O4-S2; Mol wt: 560.47

ACTION – Cephalosporin antibacterial agent active against methicillin-resistant *Staphylococcus aureus* *in vitro* (MRSA; MIC = 2 μg/ml) and *in vivo* in a murine MRSA systemic infection model (PD₅₀ = 1-4 mg/kg). Other quaternary ammonium cephalosporins include the following:



Compound	R1	Formula
256891	5-OH-2-isoquinolinium	C ₂₅ H ₁₉ Cl ₂ N ₃ O ₅ S ₂
256892	5-(NH ₂ COCH ₂ O)-2-isoquinolinium	C ₂₇ H ₂₂ Cl ₂ N ₄ O ₆ S ₂
256893	1 <i>H</i> -imidazo[4,5- <i>b</i>]pyridinium-4-yl	C ₂₂ H ₁₇ Cl ₂ N ₅ O ₄ S ₂

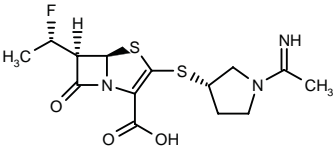
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Kim, O.K. et al. *Synthesis and structure-activity relationship of C-3 quaternary ammonium cephalosporins exhibiting anti-MRSA activities*. Bioorg Med Chem Lett 1997, 7(21): 2753.

255734

(5*R*,6*S*)-6-[1(*S*)-Fluoroethyl]-2-[1-(iminoethyl)pyrrolidin-3(*S*)-ylsulfanyl]-2-penem-3-carboxylic acid



C14-H18-F-N3-O3-S2; Mol wt: 359.43

SOURCE – Chiron.

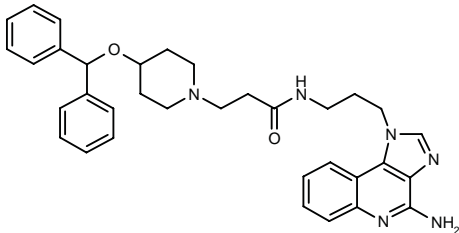
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MISCELLANEOUS DERMATOLOGIC DRUGS

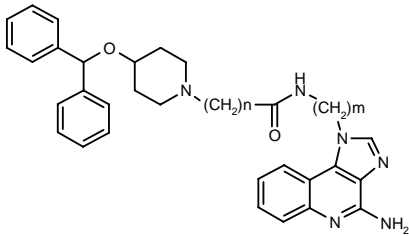
255496

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SOURCE – Terumo.

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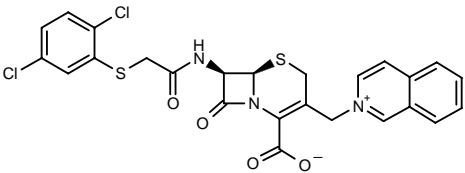
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ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

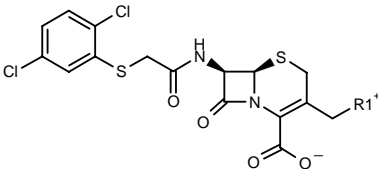
256890

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256892	5-(NH ₂ COCH ₂ O)-2-isoquinolinium	C ₂₇ H ₂₂ Cl ₂ N ₄ O ₆ S ₂
256893	1 <i>H</i> -imidazo[4,5- <i>b</i>]pyridinium-4-yl	C ₂₂ H ₁₇ Cl ₂ N ₅ O ₄ S ₂

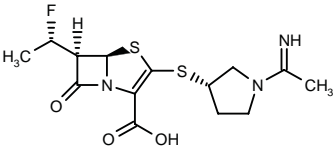
SOURCE – Bristol-Myers Squibb.

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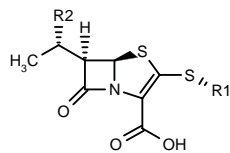
255734

(5*R*,6*S*)-6-[1(*S*)-Fluoroethyl]-2-[1-(iminoethyl)pyrrolidin-3(*S*)-ylsulfanyl]-2-penem-3-carboxylic acid



C14-H18-F-N3-O3-S2; Mol wt: 359.43

ACTION – Penem antibacterial agent active against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* 209P JC-1 (MIC = 0.05 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC = 1.56 µg/ml) and methicillin-resistant *S. aureus* 31 and 33 (MIC = 3.13 µg/ml for both). Other compounds from this series of penem derivatives include:



Compound	R1	R2	Formula
256661	CH2Ph	OH	C ₁₅ H ₁₅ NO ₄ S ₂
256662	2-indanyl	OH	C ₁₇ H ₁₇ NO ₄ S ₂
256663	1-indanyl	OH	C ₁₇ H ₁₇ NO ₄ S ₂
256664	(S)-1-Ph-3-pyrrolidinyl	F	C ₁₈ H ₁₉ FN ₂ O ₃ S ₂

SOURCE – Suntory.

REFERENCES

1. Ishiguro, S. et al. (Suntory, Ltd.) *Penem derivs. and antibacterial agents containing them*. JP 97202789.

FAROPENEM SODIUM

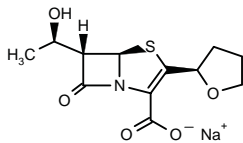
Rec INNM

127087

(5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[2(*R*)-tetrahydrofuryl]-penem-3-carboxylic acid monosodium salt

[5*R*-[3(*R*^{*}),5α,6α(*R*^{*})]]-6-(1-Hydroxyethyl)-7-oxo-3-(tetrahydro-2-furanyl)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt

ALP-201
BLA-857
RU-67655
SUN-5555⁺
SY-5555
Wy-49605
YM-044



C12-H14-N-Na-O5-S; Mol wt: 307.30

ACTION – Oral penem antibacterial agent.

INDICATION – Treatment of infections caused by faropenem-susceptible strains of *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus faecalis*, *Moraxella* (*Branhamella*) *catarrhalis*, *Escherichia coli*, *Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Proteus mirabilis*, *Haemophilus influenzae*, *Peptostreptococcus* spp., *Propionibacterium acnes* and *Bacteroides* spp.

PRESENTATION – Tablets, 150 and 200 mg.

PROPRIETARY NAME – Farom (JP).

SOURCES – Suntory; Yamanouchi.

RECENT REFERENCES

1. Boswell, F.J. et al. *Pharmacodynamic properties of faropenem demonstrated by studies of time-kill kinetics and postantibiotic effect*. J Antimicrob Chemother 1997, 39(3): 415.

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3. Devaster, J.-M. *In vitro activity of faropenem (RU67655), ketolides RU004 and 647 and five other antibiotics against Campylobacter spp*. 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst F222.

4. Dubreuil, L. et al. *Comparative in vitro activity of faropenem and other antimicrobial agents against 462 clinical anaerobes*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-222.

5. Fujii, R. et al. *Basic and clinical studies of faropenem in pediatric infection*. Jpn J Chemother 1997, 45(10): 872.

6. Fujitani, T. et al. *The nephrotoxicity of faropenem sodium in rats and dogs in combination with furosemide*. Jpn Pharmacol Ther 1997, 25(7): 33.

7. Glupczynski, Y. et al. *Comparative in vitro activity of faropenem and of ketolides against recent Belgian clinical isolates of Helicobacter pylori*. 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst E59.

8. Kanai, Y. et al. *Effects of cisplatin on pharmacokinetics of faropenem sodium, a novel penem antibiotic, in rats*. Jpn Pharmacol Ther 1997, 25(9): 129.

9. Koyama, S. *Antibiotic activity of new oral penem antibiotic, faropenem sodium and its clinical efficacy to patients with respiratory infection diseases*. J New Rem Clin 1997, 46(10): 21.

10. Le Noc, P. et al. *In vitro antibacterial activity of faropenem (RU 67655) on Enterobacteriaceae susceptible or resistant to betalactams*. 7th Int Cong Infect Dis (June 10-13, Hong Kong) 1996, Abst 113.015.

11. Marchese, A. *Antimicrobial profile of faropenem, a new oral penem*. Clin Microbiol Infect 1997, 3(Suppl. 2): Abst P703.

12. Matsuzaki, K. et al. *In vitro activities of faropenem and three oral antibiotics against 500 bacterial clinical isolates*. Jpn J Chemother 1997, 45(11): 965.

13. Saito, A. et al. *Significant role of penem antibiotics: Focused on faropenem*. Jpn J Antibiot 1997, 50(7): 1.

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17. *Product development status*. Suntory Co., Ltd. Company Communication 1997, April 30.

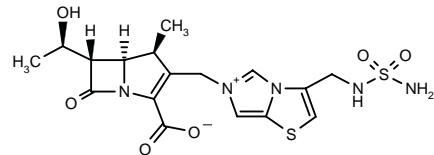
MONOGRAPH – Prous, J. et al. *SUN-5555*. Drugs Fut 1993, 18(6): 525.

⁺Annu Drug Data Rep 1987, 9(7): 619.

CP-0569*

249711

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[3-(sulfamoylaminomethyl)imidazo[5,1-*b*]thiazolium-6-ylmethyl]-1-carba-2-penem-3-carboxylate



C17-H21-N5-O6-S2; Mol wt: 455.50

ACTION – Carbapenem antibacterial agent with potent and broad-spectrum activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P JC-1, methicillin-resistant *S. aureus* M126, *Escherichia coli* NIHJ JC-2, *Pseudomonas aeruginosa* GN 10362 and imipenem/ceftazidime-resistant *P. aeruginosa* PRC-85; it showed MIC values less than or equal to those of imipenem when tested against the above-mentioned strains (MIC < 0.025, 6.25, 0.20, 1.56 and 6.25 µg/ml, respectively, vs. < 0.025, 50, 0.10, 1.56 and 25 µg/ml, respectively). The compound is very stable in the presence of renal dehydropeptidase-I (DHP-I).

SOURCE – Meiji Seika.

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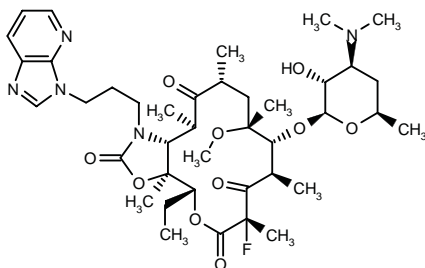
2. Kano, Y. et al. *Synthesis and antibacterial activity of novel carbapenem derivatives bearing imidazo[5,1-b]thiazole*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-03.

*Identified compound **249711** published with incorrect molecular formula Annu Drug Data Rep 1997, 19(7): 636.

MISCELLANEOUS ANTIBIOTICS

256335

11-*N*,12-*O*-Carbonyl-11-deoxy-3-de(2,6-dideoxy-3-*C*,3-*O*-dimethyl- α -L-ribohexopyranosyloxy)-2-fluoro-11-[4-(3*H*-imidazo[4,5-*b*]pyridin-3-yl)butylamino]-6-*O*-methyl-3-oxo-erythromycin A



C40-H60-F-N5-O10; Mol wt: 789.94

ACTION – Antibacterial agent particularly active against Gram-positive bacteria such as *Staphylococcus aureus* O11UC4 (MIC = 0.04 µg/ml) and *Streptococcus faecalis* D02D2UC1 (MIC = 0.02 µg/ml); also active against Gram-negative bacteria including *Haemophilus influenzae* 351HT3, 351CB12, 351CA1 and 351GR6. Preferably for oral administration.

SOURCE – Hoechst Marion Roussel.

REFERENCES

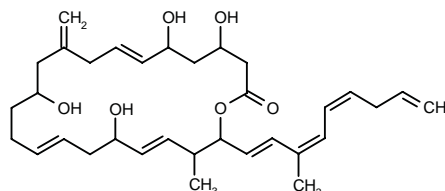
1. Agouridas, C. et al. (Roussel Uclaf) *Erythromycin derivs., their production and their use as medicaments*. EP 799833, JP 97176182.

YM-32890A

253747

4,6,12,18-Tetrahydroxy-21-methyl-10-methylene-22-[3-methyl-1(*E*),3(*Z*),5(*Z*),8-nonatetraenyl]oxacyclodocosa-7(*E*),15(*E*),19(*E*)-trien-2-one

YL-02905S-B



C33-H48-O6; Mol wt: 540.74

Colorless syrup.

ACTION – Macrolide antibiotic isolated from the culture broth of *Cytophaga* sp. YL-02905S (FERM P-13370) that shows potent activity against staphylococci including macrolide- and methicillin-resistant *Staphylococcus aureus* (MIC = 0.4 and 0.2 µg/ml, respectively), but no activity against other Gram-positive or Gram-negative bacteria or yeasts. The antibiotic was cytotoxic to L1210 cells with an IC₅₀ of 15.7 µg/ml.

SOURCES – P.T. Kalbe Farma; Yamanouchi.

REFERENCES

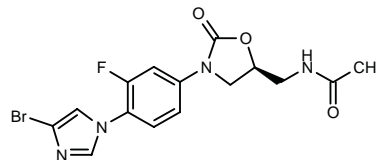
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MISCELLANEOUS ANTIBACTERIAL AGENTS

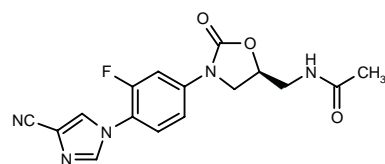
255621

N-[3-[4-(4-Bromoimidazol-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C15-H14-Br-F-N4-O3; Mol wt: 397.20

ACTION – Oxazolidinone antibacterial agent with activity *in vitro* against Gram-positive organisms including *Staphylococcus aureus* Oxford (MIC = 0.125 µg/ml), methicillin-resistant/quinolone-resistant *S. aureus* (MIC = 0.5 µg/ml), coagulase-negative staphylococci (MIC = 0.06 µg/ml) and *Enterococcus faecalis* (MIC = 0.25 µg/ml). Another specifically claimed substituted phenyloxazolidinone is:



256553: C16-H14-F-N5-O3

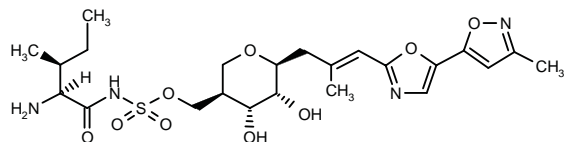
SOURCE – Zeneca.

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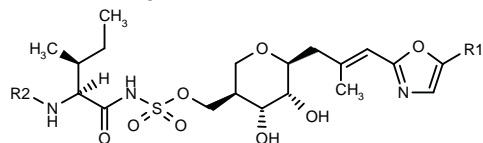
256209

N-(*L*-Isoleucyl)sulfamic acid 4(*R*),5(*R*)-dihydroxy-6(*S*)-[2-methyl-3-[5-(3-methylisoxazol-5-yl)oxazol-2-yl]-2(*E*)-propenyl]tetrahydropyran-3(*R*)-yl ester

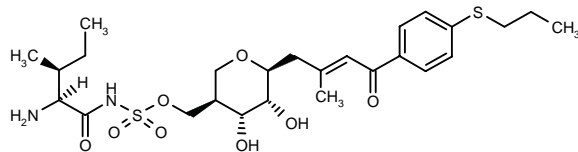


C23-H34-N4-O9-S; Mol wt: 542.60

ACTION – Antibacterial agent that acts by inhibiting protein synthesis through reversible and selective inhibition of isoleucyl-tRNA synthetase (isoleucine-tRNA ligase) from a range of Gram-positive and Gram-negative organisms including methicillin-resistant *Staphylococcus aureus*. MICs were in the range 1-32 µg/ml against several representative strains of *Streptococcus pneumoniae*. Other specifically claimed compounds with a sulfamoyl group include the following:



Compound	R1	R2	Formula
257461	Ph	H	C ₂₅ H ₃₅ N ₃ O ₈ S
257462	4-CN-2-furyl	H	C ₂₄ H ₃₂ N ₄ O ₉ S
257463	4-(MeSO ₂)-Ph	H	C ₂₆ H ₃₇ N ₃ O ₁₀ S ₂
257464	4-MeS-Ph	H	C ₂₆ H ₃₇ N ₃ O ₈ S ₂
257465	4-Cl-3-Pyr	H	C ₂₄ H ₃₃ ClN ₄ O ₈ S
257466	4-Me-Ph	H	C ₂₆ H ₃₇ N ₃ O ₈ S
257467	4-(MeSO)-Ph	H	C ₂₆ H ₃₇ N ₃ O ₉ S ₂
257468	4-Me-Ph	H-L-Phe-	C ₃₅ H ₄₆ N ₄ O ₉ S



257460: C26-H40-N2-O8-S2

SOURCE – SmithKline Beecham.

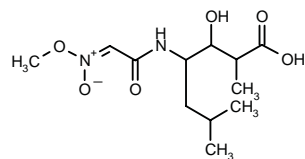
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A-76356

255731

3-Hydroxy-4-[2-(*N*-methoxy-*N*-oxidoimino)acetamido]-2,6-dimethylheptanoic acid



C12-H22-N2-O6; Mol wt: 290.32

ACTION – Antibacterial agent isolated from *Micromonospora* sp. SANK 62395 (FERM BP-5287), active against *Staphylococcus aureus* 209P JC-1, methicillin-resistant *S. aureus* 535, *Bacillus subtilis* ATCC 6633, *Enterococcus faecalis* 681 and *Klebsiella pneumoniae* 806, with respective MIC values of 25, 50, 50, 25 and 50 µg/ml.

SOURCE – Sankyo.

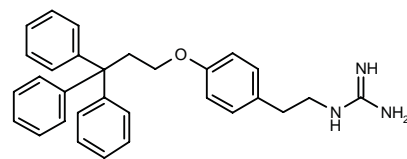
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RWJ-49815

253554

N-[2-[4-(3,3,3-Triphenylpropoxy)phenyl]ethyl]guanidine



C30-H31-N3-O; Mol wt: 449.59

ACTION – Antibacterial agent, an inhibitor of the bacterial two-component regulatory system, as demonstrated using the KinA/SpoOF system of *Bacillus subtilis* (IC₅₀ = 4 µM for inhibition of the autophosphorylation of the bacterial kinase KinA). It demonstrated potent activity against methicillin-resistant *Staphylococcus aureus* OC 2089 and vancomycin-resistant *Enterococcus faecium* OC 3312 (MIC = 1 µg/ml for both), as well as against methicillin-susceptible *S. aureus* ATCC 29213 and *Enterococcus faecalis* OC 3041 (MIC = 2 µg/ml for both strains).

SOURCES – Ortho; R.W. Johnson Pharm. Res. Inst.

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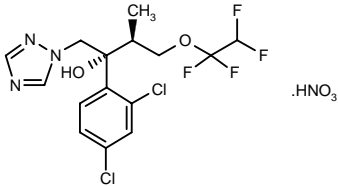
2. Demers, J.P. et al. *The identification of RWJ-49815, a novel inhibitor of bacterial two-component regulatory systems and a potent Gram positive antibacterial*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-227.

3. Lawrence, L. et al. *Investigation of the mechanism of action of a novel two-component system inhibitor*. 97th Gen Meet Amer Soc Microbiol (May 4-8, Miami Beach) 1997, Abst A-56.

ANTIFUNGAL AGENTS

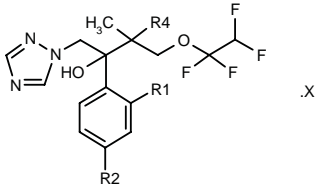
255616

(-)-(2*R*,3*S*)-2-(2,4-Dichlorophenyl)-3-methyl-4-(1,1,2,2-tetrafluoroethoxy)-1-(1,2,4-triazol-1-yl)-2-butanol nitrate



C15-H15-Cl2-F4-N3-O2.H-N-O3; Mol wt: 479.21

ACTION – Antifungal agent with potent *in vitro* activity against yeasts, filamentous fungi, dermatophytes and dimorphic fungi including *Candida albicans* 1040 (IC₅₀ = 0.0078 µg/ml), *Cryptococcus neoformans* (IC₅₀ = 0.0078 µg/ml), *Trichophyton mentagrophytes* (MIC = 0.0625 µg/ml) and *Aspergillus fumigatus* (MIC = 2 µg/ml); the reference compound fluconazole gave respective IC₅₀/MIC values of 0.5, 2, 16 and > 128 µg/ml. *In vivo* activity was demonstrated in a series of experimental models in mice infected with *C. albicans* 1040 (systemic; PD₅₀ = 0.38 mg/kg p.o.), *C. neoformans* 3443 (systemic; PD₅₀ = 5.48 mg/kg p.o.), *C. neoformans* ISM (intracranial; PD₅₀ = 12.5 mg/kg p.o.), *A. fumigatus* MOL-4 (pulmonary; PD₅₀ = 6.9 mg/kg p.o.) and *A. fumigatus* MOL-4 (systemic; PD₅₀ = 4.5 mg/kg p.o.); fluconazole was markedly less potent in the model of systemic cryptococcosis (PD₅₀ = 63.16 mg/kg p.o.) and was inactive against pulmonary aspergillosis (PD₅₀ > 60 mg/kg p.o.). Other representative compounds within this series of azole derivatives include the following:



Compound	R1=R2	R3	Isomer	X	Formula
256484	F	Me	(-)		C ₁₆ H ₁₇ F ₆ N ₃ O ₂
256485	F	Me	(+)		C ₁₆ H ₁₇ F ₆ N ₃ O ₂
256486	F	H	2 <i>R</i> ,3 <i>S</i>	HNO ₃	C ₁₅ H ₁₅ F ₆ N ₃ O ₂ .HNO ₃
256487	Cl	H	2 <i>S</i> ,3 <i>R</i>	HNO ₃	C ₁₅ H ₁₅ Cl ₂ F ₄ N ₃ O ₂ .HNO ₃

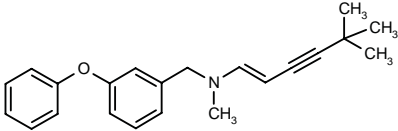
SOURCE – Zambon.

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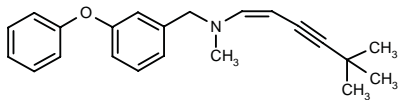
255732

N-[5,5-Dimethylhex-1 (*E*)-en-3-ynyl]-*N*-methyl-*N*-(3-phenoxybenzyl)amine



C22-H25-N-O; Mol wt: 319.45

ACTION – Antifungal agent with MIC values of 100 µg/ml when assessed *in vitro* against *Trichophyton mentagrophytes* TIMM1189 and *Trichophyton rubrum* IFO5808. Another exemplified diphenyl ether derivative is:



256609: C22-H25-N-O

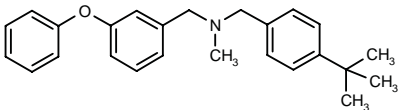
SOURCE – Pola.

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255733

N-(4-*tert*-Butylbenzyl)-*N*-methyl-*N*-(3-phenoxybenzyl)-amine



C25-H29-N-O; Mol wt: 359.51

ACTION – Antifungal agent with activity against *Trichophyton mentagrophytes* TIMM1189 (MIC = 100 µg/ml) and *Trichophyton rubrum* IFO5808 (MIC = 100 µg/ml).

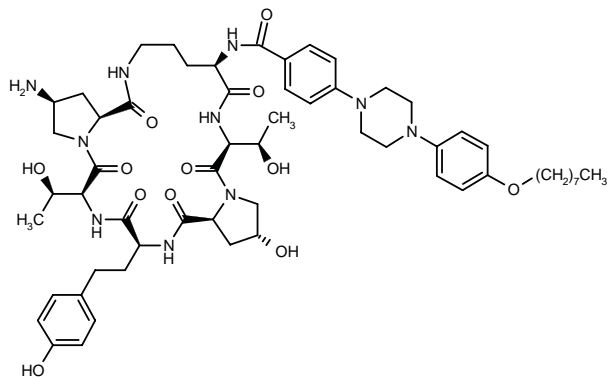
SOURCE – Pola.

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1. Kawazu, Y. et al. (Pola Chem. Ind., Inc.) Antifungal agent. JP 97208537.

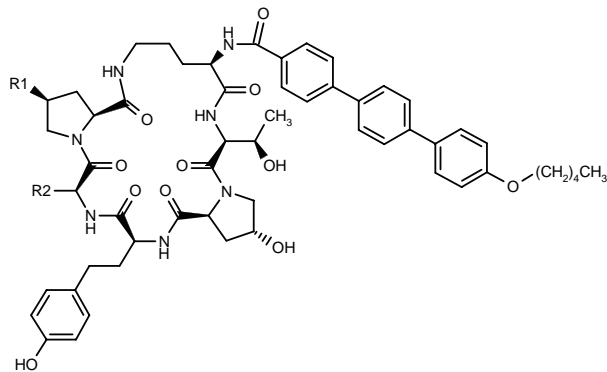
257616

[2*R*-(2α,6β,9β,14α,16β,20β,23β,25α)]-*N*-[16-Amino-2-hydroxy-6,20-bis[1(*R*)-hydroxyethyl]-23-[2-(4-hydroxyphenyl)ethyl]-5,8,14,19,22,25-hexaoxoperhydrodipyrrolo[2,1-*c*:2',1'- Π][1,4,7,10,13,16]hexaazacycloheneicosin-9-yl]-4-[4-(4-octyloxyphenyl)piperazin-1-yl]benzamide



C58-H82-N10-O12; Mol wt: 1111.35

ACTION – Antifungal agent, an inhibitor of β -1,3-glucan synthase reported to possess improved water solubility over related compounds. It exhibited potent *in vitro* activity against *Candida albicans* ATCC 10231 and ATCC 38247, with MIC values of 0.2 μ g/ml. *In vivo* activity was demonstrated in a murine model of acute systemic *C. albicans* CAF2 infection (ED₅₀ = 4.81 mg/kg i.p.). Other cyclic hexapeptides include the following:



Compound	R1	R2	Formula
258086	NH2	(CH2)3NHC(=NH)NH2	C ₅₉ H ₇₇ N ₁₁ O ₁₁
258087	NHCH2Ph	(<i>R</i>)-CH(OH)Me	C ₆₄ H ₇₈ N ₈ O ₁₂
258088	NHCOCH2N(Me) ₃ ⁺ I ⁻	(<i>R</i>)-CH(OH)Me	C ₆₂ H ₈₂ IN ₉ O ₁₃

SOURCE – Abbott.

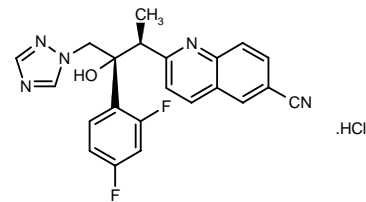
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FR-177760

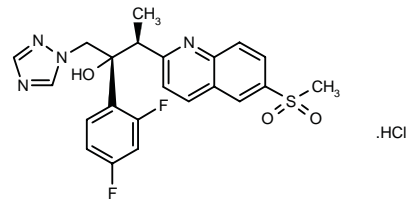
257621

(2*R*,3*S*)-3-(6-Cyanoquinolin-2-yl)-2-(2,4-difluorophenyl)-1-(1,2,4-triazol-1-yl)-2-butanol hydrochloride



C22-H17-F2-N5-O.HCl; Mol wt: 441.87

ACTION – Antifungal agent, an orally active triazole derivative with a quinoline group and *in vitro* activity against *Candida albicans* FP633 and *Aspergillus fumigatus* FP1305 (MIC = 0.0065 μ g/ml or less and 0.78 μ g/ml, respectively); it was more active than fluconazole and itraconazole against systemic candidosis and aspergillosis in mice (ED₅₀ = 0.225 and 9.92 mg/kg p.o., respectively). Another related azole is:



FR-177883 [257622]: C22-H20-F2-N4-O3-S.HCl

SOURCE – Fujisawa.

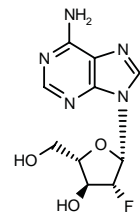
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ANTIVIRAL DRUGS

254292

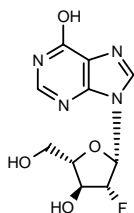
9-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)adenine



C10-H12-F-N5-O3; Mol wt: 269.23

White crystals, m.p. 231-3 °C.

ACTION – Antiviral agent, a purine nucleoside with activity against hepatitis B virus (HBV; $EC_{50} = 1.5 \mu\text{M}$ in HepG2 2.2.15 cells) and no significant cytotoxicity ($IC_{50} > 200 \mu\text{M}$ in CEM cells). Another related 9-(2-deoxy-2-fluoro- β -L-arabinofuranosyl)purine nucleoside is:



254293: C10-H11-FN4-O4

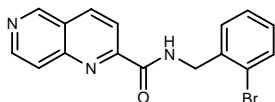
SOURCES – Univ. Georgia, Athens, GA (US); Yale Univ., New Haven, CT (US).

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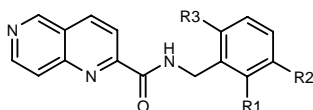
256163

N-(2-Bromobenzyl)-1,6-naphthyridine-2-carboxamide

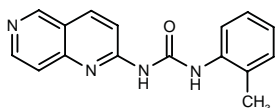


C16-H12-Br-N3-O; Mol wt: 342.19

ACTION – Antiviral agent, a potent inhibitor of human cytomegalovirus ($IC_{50} < 1 \mu\text{g/ml}$) with low cytotoxicity ($CC_{50} > 100 \mu\text{g/ml}$). Other compounds from this series of naphthyridine derivatives include the following:



Compound	R1	R2	R3	Formula
256946	Cl	H	H	C ₁₆ H ₁₂ ClN ₃ O
256947	H	OMe	H	C ₁₇ H ₁₅ N ₃ O ₂
256948	CF ₃	H	H	C ₁₇ H ₁₂ F ₃ N ₃ O
256949	OMe	H	OMe	C ₁₈ H ₁₇ N ₃ O ₃



256950: C16-H14-N4-O

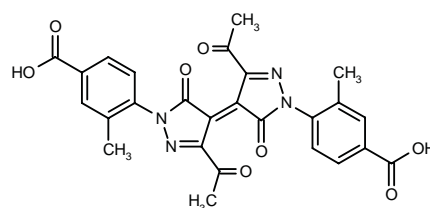
SOURCE – BioChem Pharma.

REFERENCES

- Jin, H. et al. (BioChem Pharma, Inc.) *Naphthyridine derivs. and their analogues inhibiting cytomegalovirus*. WO 9734894.

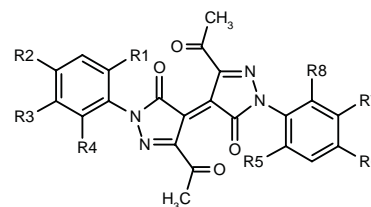
256302

4,4'-Bis[3-acetyl-1-(4-carboxy-2-methylphenyl)-4,5-dihydro-1H-pyrazol-4-ylidene]-5,5'-dione



C26-H20-N4-O8; Mol wt: 516.47

ACTION – Antiviral agent for the treatment and prophylaxis of influenza virus infections, shown to inhibit influenza A/WSN virus transcription with an IC_{50} value of $0.2 \mu\text{M}$. Antiviral activity was demonstrated against influenza A/WSN and influenza A/Victoria strains with IC_{50} values of 50 and $25 \mu\text{M}$, respectively. A representative compound from a series of pyrazole dimers, wherein the following are also included:



Compound	R1=R5	R2=R6	R3=R7	R4=R8	Formula
257973	H	CO ₂ H	H	OMe	C ₂₆ H ₂₀ N ₄ O ₁₀
257974	H	CO ₂ H	Cl	H	C ₂₄ H ₁₄ Cl ₂ N ₄ O ₈
257975	H	CO ₂ H	H	H	C ₂₄ H ₁₆ N ₄ O ₈
257976	H	H	CO ₂ H	H	C ₂₄ H ₁₆ N ₄ O ₈
257977	H	Cl	CO ₂ H	H	C ₂₄ H ₁₄ Cl ₂ N ₄ O ₈
257978	Me	H	CO ₂ H	H	C ₂₆ H ₂₀ N ₄ O ₈

SOURCE – Viropharma.

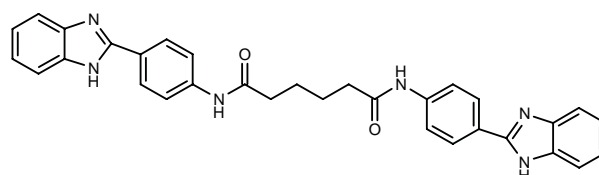
REFERENCES

- Diana, G.D. et al. (Viropharma, Inc.) *Pyrazole dimers compsns. and methods for treating influenza*. US 5684024.

257154

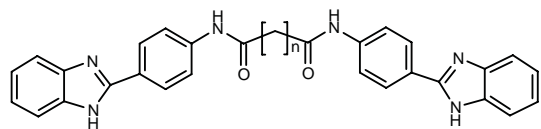
N,N'-Bis[4-(2-benzimidazolyl)phenyl]adipamide

N,N'-Bis[4-(2-benzimidazolyl)phenyl]hexanediamide

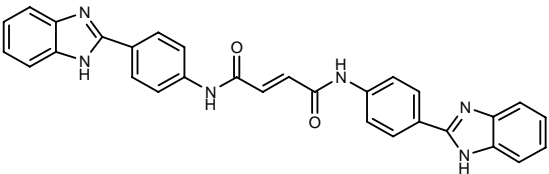


C32-H28-N6-O2; Mol wt: 528.61

ACTION – Antiviral agent for the treatment and prophylaxis of hepatitis C virus infections with inhibitory activity against the enzyme helicase ($IC_{50} = 0.7 \mu\text{M}$). Within this series of specifically claimed heterocyclic substituted carboxamides, the following are also included:



Compound	n	Formula
257687	2	C ₃₀ H ₂₄ N ₆ O ₂
257688	6	C ₃₄ H ₃₂ N ₆ O ₂
257689	7	C ₃₅ H ₃₄ N ₆ O ₂
257690	8	C ₃₆ H ₃₆ N ₆ O ₂



257691: C30-H22-N6-O2

SOURCE – Viropharma.

REFERENCES

1. Diana, G.D. and Bailey, T.R. (Viropharma, Inc.) *Cpds., compsns. and methods for treatment of hepatitis C*. WO 9736866.

INTERFERON ALFACON-1

Prop INN

198462

N-L-Methionyl-22-L-arginine-76-L-alanine-78-L-aspartic acid-79-L-glutamic acid-86-L-tyrosine-90-L-tyrosine-156-L-threonine-157-L-asparagine-158-L-leucine-interferon α_1 (human lymphoblast reduced)

Consensus interferon
rConINF
YM-643

ACTION – Non-naturally occurring, recombinant type 1 interferon.

INDICATION – Treatment of chronic hepatitis C virus (HCV) infection.

PRESENTATION – Single-use vials for s.c. injection, 9 μ g (0.3 ml) and 15 μ g (0.5 ml).

PROPRIETARY NAME – *Infergen* (US).

SOURCE – Amgen.

RECENT REFERENCES

1. Craig, J.R. et al. *Liver histology improvement is associated with ALT and HCV RNA response following treatment with consensus interferon (CIFN)*. Gastroenterology 1996, 110(4, Suppl.): A1175.

2. Hollinger, F.B. et al. *Differential response to treatment with consensus interferon (CIFN) and IFN-alpha 2b in chronic HCV patients infected with genotype 1a and 1b*. Gastroenterology 1996, 110(4, Suppl.): A1213.

3. Ip, A.Y. et al. *Stability of recombinant consensus interferon to air-jet and ultrasonic nebulization*. J Pharm Sci 1996, 84(10): 1210.

4. Klein, M.L. et al. *Structural characterization of recombinant consensus interferon- α* . J Chromatogr 1988, 454: 205.

5. Somaratne, K.D. et al. *Pharmacokinetics of recombinant consensus interferon in mice, hamsters, rats, and rhesus monkeys*. Pharm Res 1994, 11(10, Suppl.): Abst PPDM 8091.

6. Tong, M.J. et al. *Retreatment of patients with chronic hepatitis C virus infection with consensus interferon: Results of a maintenance study*. Gastroenterology 1995, 108(4, Suppl.): A1188.

7. Tong, M.J. et al. *Long-term follow-up of chronic hepatitis C virus infected patients treated with consensus interferon*. Gastroenterology 1995, 108(4, Suppl.): A1188.

8. Tong, M.J. et al. *Treatment of chronic hepatitis C with consensus interferon: A multi-center, randomized, controlled trial*. Hepatology 1997, 26(3): 747.

9. Amgen and Yamanouchi announce consensus interferon license. Amgen Inc. Press Release 1996, June 13.

10. Amgen and Yamanouchi to collaborate on Infergen. Prous Science Daily Essentials 1996, June 21.

11. Amgen: Q3 1997 highlights. Prous Science Daily Essentials October 30, 1997.

12. Amgen's Infergen(R) cleared for marketing by FDA, providing a new treatment option to hepatitis C patients. Amgen, Inc. Press Release 1997, October 7.

13. First approval for Infergen. Prous Science Daily Essentials October 8, 1997.

14. Infergen NDA filed in U.S. Prous Science Daily Essentials 1996, April 26.

15. Interferon alfacon-1 launch. Amgen, Inc. Company Communication 1997, November 25.

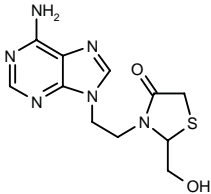
16. New product intros. Drug News Perspect 1997, 10(10): 621.

AIDS MEDICINES

256160

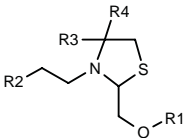
9-[2-[2-(Hydroxymethyl)-4-oxothiazolidin-3-yl]ethyl]adenine

3-[2-(Adenin-9-yl)ethyl]-2-(hydroxymethyl)thiazolidin-4-one



C11-H14-N6-O2-S; Mol wt: 294.33

ACTION – Antiviral agent for the treatment of AIDS or hepatitis B virus (HBV) infection; it gave an IC₅₀ of 5 \pm 4 μ M when tested *in vitro* against HIV-1, with low cytotoxic potential (CC₅₀ = 100 μ M in uninfected MT-4 cells; selectivity index > 20). It also inhibited HBV replication in transfected 2.2.15 cells (EC₅₀ = 0.5-2 μ M), with a low cytotoxic liability (CC₅₀ = 150 μ M). Other specifically claimed substituted 1,3-thiazolidines and 1,3-thiazolidin-4-ones include the following:



Compound	R1	R2	R3	R4	Formula
257434	COPh	cytosin-1-yl	-O-	-O-	C ₁₇ H ₁₈ N ₄ O ₄ S
257435	COPh	5-F-cytosin-1-yl	-O-	-O-	C ₁₇ H ₁₇ FN ₄ O ₄ S
257436	COPh	thymine-1-yl	-O-	-O-	C ₁₈ H ₁₉ N ₃ O ₅ S
257437	COPh	adenine-9-yl	-O-	-O-	C ₁₈ H ₁₈ N ₆ O ₃ S
257438	H	cytosin-1-yl	-O-	-O-	C ₁₀ H ₁₄ N ₄ O ₃ S

Compound	R1	R2	R3	R4	Formula
257439	H	5-F-cytosin-1-yl	-O-		C ₁₀ H ₁₃ FN ₄ O ₃ S
257440	H	thymine-1-yl	-O-		C ₁₁ H ₁₅ N ₃ O ₄ S
257441	COPh	cytosine-1-yl	H	H	C ₁₇ H ₂₀ N ₄ O ₃ S
257442	COPh	5-F-cytosine-1-yl	H	H	C ₁₇ H ₁₉ FN ₄ O ₃ S
257443	H	cytosine-1-yl	H	H	C ₁₀ H ₁₆ N ₄ O ₂ S
257444	H	5-F-cytosine-1-yl	H	H	C ₁₀ H ₁₅ FN ₄ O ₂ S

SOURCE – INSERM.

REFERENCES

1. Kraus, J.-L. et al. (INSERM) *Subst. 1,3-thiazolidines and 1,3-thiazolidin-4-ones, method for preparing same, and use thereof as drugs.* WO 9734891.

256314

Alkaline extract of *Aspalathus linearis*

ACTION – Antiviral agent with activity against HIV and other viruses such as influenza and herpes simplex viruses, an alkaline extract from the leaves, stems and/or roots of the plant *Aspalathus linearis*. Compound also exhibited antitumor activity.

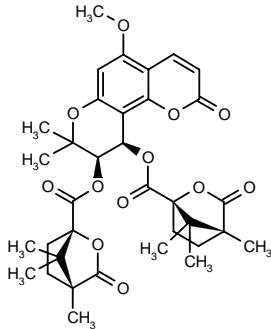
SOURCE – Mitsui Norin.

REFERENCES

1. Nakano, M. (Mitsui Norin Co., Ltd.) *An anti-viral and anti-cancer agent from "Aspalathus Linearis".* EP 796620.

256677

(9*R*,10*R*)-5-Methoxy-8,8-dimethyl-9,10-bis[4(*R*),7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1(*S*)-ylcarbonyloxy]-9,10-dihydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-2-one



C35-H40-O12; Mol wt: 652.69

M.p. 168-70 °C, [α]_D −4.44° (c 0.45, CHCl₃).

ACTION – Anti-HIV agent with potent activity against HIV-1 replication in acutely infected H9 lymphocytes (EC₅₀ = 0.138 nM), being more potent than zidovudine while maintaining a therapeutic index greater than zidovudine (IC₅₀/EC₅₀ > 400,000).

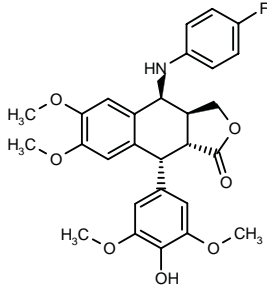
SOURCES – Biotech Res. Labs.; Univ. North Carolina, Chapel Hill, NC (US).

REFERENCES

1. Takeuchi, Y. et al. *Anti-AIDS agents -XXVIII. Synthesis and anti-HIV activity of methoxy substituted 3',4'-di-O-(-)-camphanoyl-(+)-cis-khellactone (DCK) analogues.* Bioorg Med Chem Lett 1997, 7(20): 2573.

257313

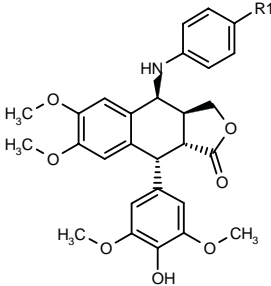
[3*aS*-(3*αα*,4*β*,9*α*,9*αβ*)]-4-(4-Fluorophenylamino)-9-(4-hydroxy-3,5-dimethoxyphenyl)-6,7-dimethoxy-1,3,3*a*,4,9,9*a*-hexahydronaphtho[2,3-*c*]furan-1-one



C28-H28-F-N-O7; Mol wt: 509.53

M.p. 221-4 °C, [α]_D²⁵ −93° (c 0.25, acetone).

ACTION – Anti-HIV agent, a podophyllotoxin derivative originally evaluated as an antineoplastic agent (IC₅₀ = 0.78 nM against KB cells). It shows potent activity against HIV-1 in H9 cells (EC₅₀ < 0.001 μM) and relatively low cytotoxicity (IC₅₀ = 0.166 μM; TI > 166). Other related compounds with a similar profile are:



Compound	R1	Formula
257310	CO ₂ Et	C ₃₁ H ₃₃ NO ₉
257311	CN	C ₂₉ H ₂₈ N ₂ O ₇
257312	NO ₂	C ₂₈ H ₂₈ N ₂ O ₉

SOURCES – Biotech Res. Labs.; Univ. North Carolina, Chapel Hill, NC (US).

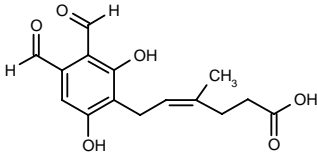
REFERENCES

1. Lee, C.T.-L. et al. *Anti-AIDS agents. 29. Anti-HIV activity of modified podophyllotoxin derivatives.* Bioorg Med Chem Lett 1997, 7(22): 2897.
2. Wang, Z.-Q. et al. *Antitumor agents. 124. New 4*β*-substituted aniline derivatives of 6,7-O,O-demethylene-4'-O-demethylpodophyllotoxin and related compounds as potent inhibitors of human DNA topoisomerase II.* J Med Chem 1992, 35(5): 871.

HERICENAL A

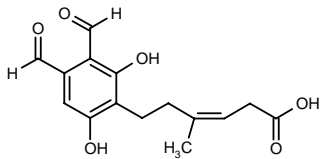
257145

6-(3,4-Diformyl-2,6-dihydroxyphenyl)-4-methyl-4(*Z*)-hexenoic acid



C15-H16-O6; Mol wt: 292.29

ACTION – Antiviral agent for AIDS with reverse transcriptase-inhibitory activity ($IC_{50} = 0.37 \mu M$), isolated from the microorganism *Hericeum erinaceus*, preferably *H. erinaceus* DSM 10600. Another inhibitor isolated from this microorganism is:



Hericenol B [257686]: C15-H16-O6

SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Stump, H. et al. (Hoechst AG) *Novel benzaldehyde derivs. from Hericeum erinaceus*. WO 9736852.

TREATMENT OF PROTOZOAL DISEASES

255192

Tyrosyl-aspartyl-glutaminy-leucyl-valyl-threonyl-arginyl-valyl-valyl-threonyl-histidyl-glutamyl-methionyl-alanyl-histidyl-alanine

C81-H128-N24-O25-S; Mol wt: 1870.11

ACTION – Immunogen selected from the primary structure of *Leishmania major*, suitable for vaccination against leishmaniasis. It was shown to stimulate murine T-lymphocyte proliferation and IL-2 and IL-3 production following stimulation of T-cells from mice, and it protected mice against the development of *L. major* and *Leishmania mexicana* lesions when given with adjuvant. Other related peptides include the following:

Threonyl-arginyl-valyl-valyl-threonyl-histidyl-glutamyl-methionyl-alanyl-histidyl-alanyl-leucyl-phenylalanyl-seryl-glycine

255367: C72-H114-N22-O21-S

Prolyl-phenylalanyl-asparaginy-valyl-phenylalanyl-seryl-aspartyl-alanyl-alanyl-arginyl-cysteinyl-isoleucyl-aspartyl-glycyl-alanyl-phenylalanine

255368: C78-H112-N20-O23-S

Valyl-arginyl-aspartyl-valyl-asparaginy-tryptophanylglycyl-alanyl-leucyl-arginyl-isoleucyl-alanyl-valyl-serine

255369: C69-H114-N22-O19

Alanyl-alanyl-arginyl-cysteinyl-isoleucyl-aspartyl-glycyl-alanyl-phenylalanyl-arginyl-prolyl-lysyl-alanyl-threonyl-aspartyl-glycine

255370: C69-H113-N23-O22-S

Arginyl-prolyl-lysyl-alanyl-threonyl-aspartyl-glycyl-isoleucyl-valyl-lysyl-seryl-tyrosyl-alanyl-glycyl-leucyl-cysteine

255371: C73-H123-N21-O22-S

Phenylalanyl-seryl-glycyl-prolyl-phenylalanyl-phenylalanyl-glutamyl-aspartyl-alanyl-arginyl-isoleucyl-valyl-alanyl-asparaginy-valyl-proline

255372: C83-H120-N20-O23

SOURCE – Univ. Victoria, Victoria (CA).

REFERENCES

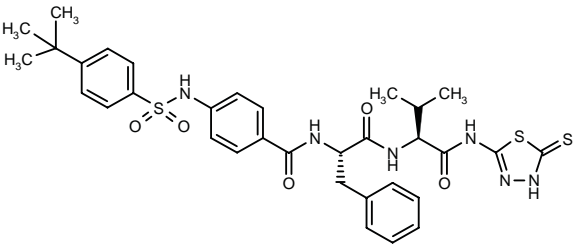
1. Olafson, R.W. (Univ. Victoria) *Peptides capable of eliciting an immune response to leishmaniasis and methods of using the same*. US 5674503.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

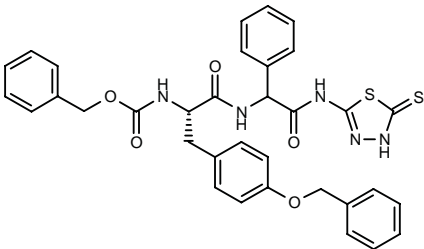
255391

5-[N-[4-(4-*tert*-Butylphenylsulfonamido)benzoyl]-L-phenylalanyl-L-valylamino]-1,3,4-thiadiazole-2(3*H*)-thione



C33-H38-N6-O5-S3; Mol wt: 694.88

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases such as stromelysin ($K_i = 44 \text{ nM}$), human neutrophil collagenase ($K_i = 1.04 \text{ nM}$) and 72-kD gelatinase ($K_i = 0.68 \text{ nM}$). Another specifically claimed amino acid amide of 5-amino-1,3,4-thiadiazole is:



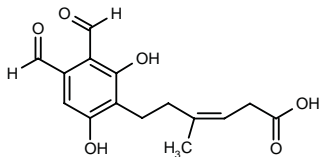
255916: C34-H31-N5-O5-S2

SOURCE – Proscript.

REFERENCES

1. Oleksyszyn, J. and Jacobson, A.R. (Proscript, Inc.) *Amino acid amides of 1,3,4-thiadiazoles as matrix metalloproteinase*. US 5677282.

ACTION – Antiviral agent for AIDS with reverse transcriptase-inhibitory activity ($IC_{50} = 0.37 \mu M$), isolated from the microorganism *Hericeum erinaceus*, preferably *H. erinaceus* DSM 10600. Another inhibitor isolated from this microorganism is:



Hericenol B [257686]: C15-H16-O6

SOURCE – Hoechst Marion Roussel.

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1. Stump, H. et al. (Hoechst AG) *Novel benzaldehyde derivs. from Hericeum erinaceus*. WO 9736852.

TREATMENT OF PROTOZOAL DISEASES

255192

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255367: C72-H114-N22-O21-S

Prolyl-phenylalanyl-asparaginy-valyl-phenylalanyl-seryl-aspartyl-alanyl-alanyl-arginyl-cysteinyl-isoleucyl-aspartyl-glycyl-alanyl-phenylalanine

255368: C78-H112-N20-O23-S

Valyl-arginyl-aspartyl-valyl-asparaginy-tryptophanylglycyl-alanyl-leucyl-arginyl-isoleucyl-alanyl-valyl-serine

255369: C69-H114-N22-O19

Alanyl-alanyl-arginyl-cysteinyl-isoleucyl-aspartyl-glycyl-alanyl-phenylalanyl-arginyl-prolyl-lysyl-alanyl-threonyl-aspartyl-glycine

255370: C69-H113-N23-O22-S

Arginyl-prolyl-lysyl-alanyl-threonyl-aspartyl-glycyl-isoleucyl-valyl-lysyl-seryl-tyrosyl-alanyl-glycyl-leucyl-cysteine

255371: C73-H123-N21-O22-S

Phenylalanyl-seryl-glycyl-prolyl-phenylalanyl-phenylalanyl-glutamyl-aspartyl-alanyl-arginyl-isoleucyl-valyl-alanyl-asparaginy-valyl-proline

255372: C83-H120-N20-O23

SOURCE – Univ. Victoria, Victoria (CA).

REFERENCES

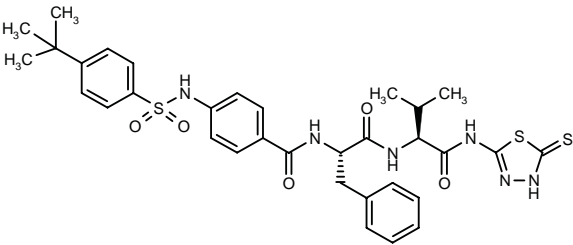
1. Olafson, R.W. (Univ. Victoria) *Peptides capable of eliciting an immune response to leishmaniasis and methods of using the same*. US 5674503.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

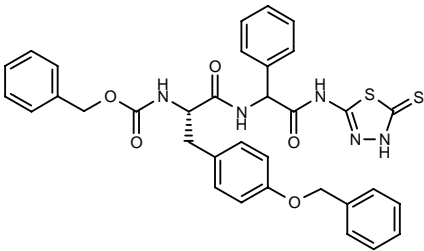
255391

5-[N-[4-(4-*tert*-Butylphenylsulfonamido)benzoyl]-L-phenylalanyl-L-valylamino]-1,3,4-thiadiazole-2(3*H*)-thione



C33-H38-N6-O5-S3; Mol wt: 694.88

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases such as stromelysin ($K_i = 44 \text{ nM}$), human neutrophil collagenase ($K_i = 1.04 \text{ nM}$) and 72-kD gelatinase ($K_i = 0.68 \text{ nM}$). Another specifically claimed amino acid amide of 5-amino-1,3,4-thiadiazole is:



255916: C34-H31-N5-O5-S2

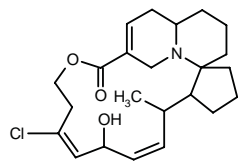
SOURCE – Proscript.

REFERENCES

1. Oleksyszyn, J. and Jacobson, A.R. (Proscript, Inc.) *Amino acid amides of 1,3,4-thiadiazoles as matrix metalloproteinase*. US 5677282.

255498

12-Chloro-1,2,3,4,10,11,14,17,17a,18,19,20-dodecahydro-14-hydroxy-17-methyl-8*H*-4,7-ethanylidene-6*H*-cyclopenta[*f*]pyrido[1,2-*e*][1,5]oxaazacyclopentadecin-8-one



C23-H32-Cl-N-O3; Mol wt: 405.96

ACTION – Agent for the treatment of rheumatoid arthritis, bronchial asthma, atherosclerosis, organ transplant rejection, sarcoidosis, inflammation and tumor metastasis isolated from the marine sponge *Halicondria okadai*, an inhibitor of TNF- α -induced VCAM-1 production (IC_{50} = 7.0 μ g/ml) in human umbilical vein endothelial cells (HUVEC), with low cytotoxicity (IC_{50} > 100 μ g/ml).

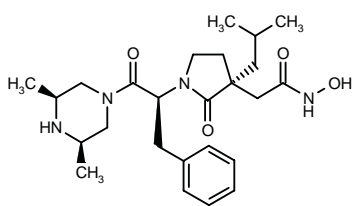
SOURCE – Sagami.

REFERENCES

1. Uemura, D. et al. (Sagami Chem. Res. Center) *Spiro[1-azabicyclo[4.4.0]deca-3-ene-9,1'-cyclopentane] derivs.* JP 97208588.

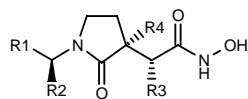
255656

2(*S*)-[1-[1(*S*)-Benzyl-2-(*cis*-3,5-dimethylpiperazin-1-yl)-2-oxoethyl]-3(*S*)-isobutyl-2-oxopyrrolidin-3-yl]acetohydroxamic acid



C25-H38-N4-O4; Mol wt: 458.60

ACTION – A potent inhibitor of matrix metalloproteinases such as collagenase (K_i = 0.00069 μ M), gelatinase (K_i = 0.00106 μ M) and stromelysin (K_i = 0.0105 μ M), with potential in the treatment of disorders related to connective tissue degradation such as osteoarthritis, rheumatoid arthritis, osteoporosis, tumor metastasis, periodontitis and corneal, dermal or gastric ulceration. Within this series of exemplified hydroxamic acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
256796	CH2Ph	4-Pyr-NHCO	H	i-Bu	C ₂₄ H ₃₀ N ₄ O ₄
256797	CH2Ph	4-F-Ph-NHCO	H	i-Bu	C ₂₅ H ₃₀ FN ₄ O ₄
256798	cyclohexyl	2-Pyr-NHCO	H	i-Bu	C ₂₃ H ₃₄ N ₄ O ₄

Compound	R1	R2	R3	R4	Formula
256799	cyclohexyl	4-F-Ph-NHCO	H	i-Bu	C ₂₄ H ₃₄ FN ₃ O ₄
256800	H	CH2Ph	3-F-PhCO-NHCH2CH2	i-Bu	C ₂₇ H ₃₄ FN ₃ O ₄
256801	H	CH2Ph	3,4-(F)2-PhCO-NHCH2CH2	(CH2)3OH	C ₂₆ H ₃₁ F ₂ N ₃ O ₅
256802	H	CH2Ph	3-F-PhCO-NHCH2CH2	(CH2)3OH	C ₂₆ H ₃₂ FN ₃ O ₅

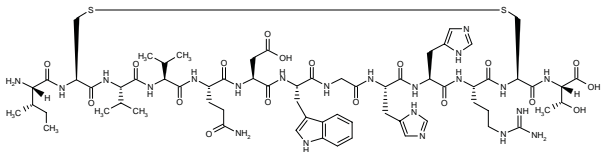
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Jacobsen, E.J. (Pharmacia & Upjohn Co.) *Hydroxamic acid derivs. for use with the treatment of diseases related to connective tissue degradation.* WO 9732846.

255697

Isoleucyl-cysteinyI-valyl-valyl-glutaminyI-aspartyl-tryptophanyl-glycyl-histidyl-histidyl-arginyl-cysteinyI-threonine cyclic (2-12)-disulfide



C66-H98-N22-O18-S2; Mol wt: 1551.76

ACTION – Peptide with inhibitory activity on complement activation that acts by binding to C3. Compound was found to inhibit both classical and alternative pathways of complement activation in human serum with IC_{50} values of 63 and 12 μ M, respectively. In another assay using purified C3, compound inhibited the proteolytic activation of C3 to C3b with an IC_{50} of 28 μ M. Potentially useful for the treatment of autoimmune diseases such as type II collagen-induced arthritis, myasthenia gravis, hemolytic anemia, glomerulonephritis and immune complex-induced vasculitis, as well as adult respiratory distress syndrome, stroke, heart attack, xenotransplantation and multiple sclerosis.

SOURCE – Univ. Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Lambris, J.D. and Sahu, A.K. (Univ. Pennsylvania) *Novel peptides which inhibit complement activation.* WO 9733603.

255788

D-Alanyl-alanyl-(cyclohexyl)alanyl-alanyl-alanyl-alanyl-alanyl-alanyl-threonyI-leucyl-lysyl-alanyl-alanyl-D-alaninamide

C55-H98-N16-O15; Mol wt: 1223.48

ACTION – Immunosuppressant peptide that binds major histocompatibility complex (MHC) molecules and inhibits HLA-DR-restricted T-cell activation, for the treatment of autoimmune diseases such as rheumatoid arthritis. Other related peptides are:

D-Alanyl-alanyl-phenylalanyl-alanyl-alanyl-alanyl-alanyl-threonyl-leucyl-lysyl-alanyl-alanyl-D-alaninamide

256017: C52-H87-N15-O14

D-Alanyl-alanyl-phenylalanyl-alanyl-alanyl-alanyl-lysyl-threonyl-alanyl-alanyl-alanyl-alanyl-D-alaninamide

256018: C49-H81-N15-O14

D-Alanyl-alanyl-phenylalanyl-alanyl-alanyl-alanyl-lysyl-threonyl-leucyl-alanyl-alanyl-alanyl-D-alaninamide

256019: C52-H87-N15-O14

D-Alanyl-alanyl-phenylalanyl-lysyl-alanyl-alanyl-threonyl-alanyl-lysyl-alanyl-alanyl-D-alaninamide

256020: C49-H83-N15-O13

Acetyl-D-alanyl-alanyl-phenylalanyl-alanyl-alanyl-alanyl-lysyl-threonyl-alanyl-alanyl-alanyl-phenylalanyl-D-alaninamide

256021: C57-H87-N15-O15

Acetyl-D-alanyl-alanyl-(cyclohexyl)alanyl-alanyl-alanyl-alanyl-lysyl-threonyl-alanyl-alanyl-alanyl-alanyl-D-alaninamide

256022: C45-H79-N15-O15

D-Alanyl-alanyl-phenylalanyl-alanyl-lysyl-alanyl-alanyl-threonyl-leucyl-lysyl-alanyl-alanyl-D-alaninamide

256023: C55-H94-N16-O14

D-Alanyl-alanyl-phenylalanyl-alanyl-alanyl-alanyl-lysyl-threonyl-alanyl-alanyl-alanyl-phenylalanyl-D-alaninamide

256024: C55-H85-N15-O14

D-Alanyl-alanyl-phenylalanyl-alanyl-alanyl-alanyl-lysyl-threonyl-alanyl-alanyl-alanyl-alanyl-alaninamide

256025: C49-H81-N15-O14

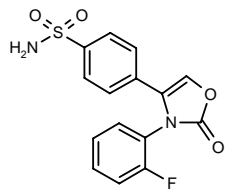
SOURCES – Cytel; Novartis.

REFERENCES

1. Gaeta, F.C.A. et al. (Cytel Corp.; Sandoz, Ltd.) *Immunosuppressant peptides*. US 5679640.

256155

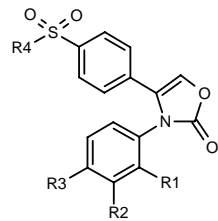
4-[3-(2-Fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide



C15-H11-F-N2-O4-S; Mol wt: 334.32

ACTION – Orally active antiinflammatory agent with potent and selective inhibitory activity against human cyclooxygenase type 2 (COX-2; IC₅₀ = 9.6 nM) relative to COX-1 (IC₅₀ = 22.6 μM). *In vivo*, it was as potent as

indomethacin in inhibiting adjuvant-induced arthritis in the rat (65 and 64% inhibition, respectively, at 1 mg/kg p.o.), while showing markedly reduced ulcerogenic potential (UD₅₀ > 100 mg/kg p.o. compared to 17 mg/kg p.o. for indomethacin). Other specifically claimed 2(3*H*)-oxazolone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
257289	H	H	F	Me	C ₁₆ H ₁₂ FNO ₄ S
257290	H	Cl	Cl	NH ₂	C ₁₅ H ₁₀ Cl ₂ N ₂ O ₄ S
257291	F	H	F	NH ₂	C ₁₅ H ₁₀ F ₂ N ₂ O ₄ S

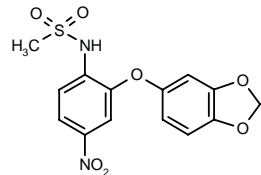
SOURCE – Almirall.

REFERENCES

1. Puig Duran, C. et al. (Grupo Farmaceut. Almirall SA) *2-(3H)-Oxazolone derivs. and their use as COX-2 inhibitors*. WO 9734882.

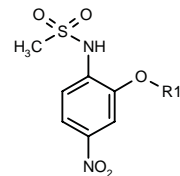
256363

N-[2-(1,3-Benzodioxol-5-yloxy)-4-nitrophenyl]methanesulfonamide



C14-H12-N2-O7-S; Mol wt: 352.32

ACTION – Nonsteroidal antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; 77% inhibition at 100 nM vs. 89% inhibition of COX-1 at 100 μM, using human recombinant enzymes). *In vivo* activity was demonstrated in the carrageenan-induced pleurisy test in the rat, giving 36% inhibition of prostaglandin production at 10 mg/kg p.o. Other compounds from this series of methanesulfonamide derivatives include the following:



Compound	R1	Formula
257931	2-Naph	C ₁₇ H ₁₄ N ₂ O ₅ S
257932	6-F-2-Naph	C ₁₇ H ₁₃ FN ₂ O ₅ S
257933	5-benzothienyl	C ₁₅ H ₁₂ N ₂ O ₅ S ₂
257934	6-benzothiazolyl	C ₁₄ H ₁₁ N ₃ O ₅ S ₂

SOURCE – Abbott.

REFERENCES

1. Dellaria, J.F. and Gane, T.H. (Abbott Labs.) *Prostaglandin synthase-2 inhibitors*. US 5681842.

[D-Pro⁵]h/r-CRF

255684

Seryl-glutamyl-glutamyl-prolyl-D-prolyl-isoleucyl-seryl-leucyl-aspartyl-leucyl-threonyl-phenylalanyl-histidyl-leucyl-leucyl-arginyl-glutamyl-valyl-leucyl-glutamyl-methionyl-alanyl-arginyl-alanyl-glutamyl-glutamyl-leucyl-alanyl-glutamyl-glutamyl-alanyl-histidyl-seryl-asparaginyal-arginyl-lysyl-leucyl-methionyl-glutamyl-isoleucyl-isoleucinamide

C208-H344-N60-O63-S2; Mol wt: 4757.49

ACTION – Antiinflammatory agent, a corticotropin-releasing factor (CRF) analog whose antiedema activity is disassociated from adrenocorticotropin (ACTH) release; it exhibits reduced agonist activity at the CRF_{2β} receptor subtype compared to CRF, but comparable activity at the CRF₁ subtype. The compound suppressed heat-induced edema in rats (ED₅₀ = 10 µg/kg i.v.) without significant concomitant release of ACTH.

SOURCE – Univ. California, Oakland, CA (US).

REFERENCES

1. Wei, E.T. et al. (Univ. California) *Anti-inflammatory CRF analogs, their compsns. and use*. WO 9732898.

IR-501

256583

Combination of three peptides derived from T-cell receptors (Vβ3, Vβ14, Vβ17) in incomplete Freund's adjuvant (IFA)

ACTION – Therapeutic vaccine for rheumatoid arthritis that consists of three T-cell receptor peptides (Vβ3, Vβ14 and Vβ17) in incomplete Freund's adjuvant and is designed to turn off the specific immune system cells believed to cause the disease. In phase II trials in patients with rheumatoid arthritis, the compound (90 or 300 µg i.m. at 0, 4, 8 and 20 weeks) was well tolerated and produced significant disease improvement.

SOURCE – Immune Response Corp.

REFERENCES

1. Brostoff, S.W. *T cell receptor peptide vaccines as immunotherapy for autoimmune disease*. IBC 3rd Annu Conf Vaccines. New Adv Technol Appl (Feb 26-27, Rockville) 1996.

2. Moreland, L. et al. *Results of phase II rheumatoid arthritis clinical trial using T cell receptor peptides*. Arthritis Rheum 1997, 40(9, Suppl.): Abst 1156.

3. Morgan, E.E. *Clinical trials using T-cell receptor peptides in autoimmune diseases*. IBC Conf Autoimmune Dis. Exploiting Mech Drug Dev Diagn (Sept 29-30, San Francisco) 1997.

4. *Immune Response announces results for rheumatoid arthritis Rx*. Prous Science Daily Essentials January 8, 1997.

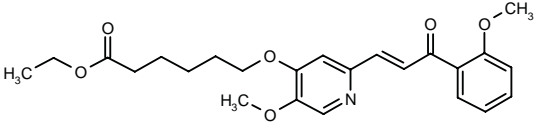
5. *Phase II results with T-cell receptor peptides in RA promising*. Prous Science Daily Essentials November 20, 1997.

6. *Phase IIb trial of TCR vaccine for rheumatoid arthritis begins*. Prous Science Daily Essentials December 29, 1997.

IMMUNOLOGIC DRUGS

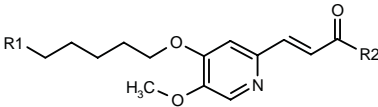
255704

6-[5-Methoxy-2-[3-(2-methoxyphenyl)-3-oxo-1 (E)-propenyl]pyridin-4-yloxy]hexanoic acid ethyl ester



C24-H29-N-O6; Mol wt: 427.50

ACTION – Cytokine production inhibitor shown to inhibit PMA-stimulated IL-4 production in human ATL-16T(-) cells (70.4% inhibition at 1 µM), as well as concanavalin A-stimulated IL-5 production in human peripheral blood lymphocytes (95.2% inhibition at 1 µM). *In vivo*, it produced a 63.4% inhibition of IgE production in *Ascaris* antigen-sensitized mice at 100 mg/kg/day p.o. for 10 days. Within this series of pyridine derivatives, the following are also included:



Compound	R1	R2	Formula
256874	CO ₂ Et	cyclohexyl	C ₂₃ H ₃₃ NO ₅
256875	CO ₂ Et	2,4-(MeO) ₂ -Ph	C ₂₅ H ₃₁ NO ₇
256876	CH ₂ CO ₂ Et	2-MeO-Ph	C ₂₅ H ₃₁ NO ₆
256877	(CH ₂) ₆ CO ₂ Et	2-MeO-Ph	C ₃₀ H ₄₁ NO ₆
256878	CO ₂ H	2-MeO-Ph	C ₂₂ H ₂₅ NO ₆

SOURCE – SS Pharm.

REFERENCES

1. Hasegawa, H. et al. (SS Pharm. Co., Ltd.) *Novel pyridine derivs. and medicines containing the same as active ingredient*. WO 9733870.

SOURCE – Abbott.

REFERENCES

1. Dellaria, J.F. and Gane, T.H. (Abbott Labs.) *Prostaglandin synthase-2 inhibitors*. US 5681842.

[D-Pro⁵]h/r-CRF

255684

Seryl-glutamyl-glutamyl-prolyl-D-prolyl-isoleucyl-seryl-leucyl-aspartyl-leucyl-threonyl-phenylalanyl-histidyl-leucyl-leucyl-arginyl-glutamyl-valyl-leucyl-glutamyl-methionyl-alanyl-arginyl-alanyl-glutamyl-glutamyl-leucyl-alanyl-glutamyl-glutamyl-alanyl-histidyl-seryl-asparaginyal-arginyl-lysyl-leucyl-methionyl-glutamyl-isoleucyl-isoleucinamide

C208-H344-N60-O63-S2; Mol wt: 4757.49

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IR-501

256583

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SOURCE – Immune Response Corp.

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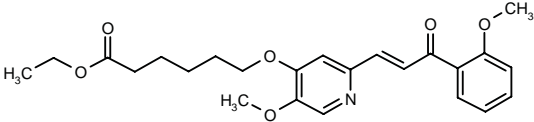
5. *Phase II results with T-cell receptor peptides in RA promising*. Prous Science Daily Essentials November 20, 1997.

6. *Phase IIb trial of TCR vaccine for rheumatoid arthritis begins*. Prous Science Daily Essentials December 29, 1997.

IMMUNOLOGIC DRUGS

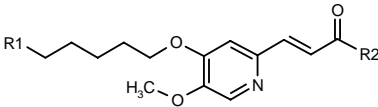
255704

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Compound	R1	R2	Formula
256874	CO2Et	cyclohexyl	C ₂₃ H ₃₃ NO ₅
256875	CO2Et	2,4-(MeO)2-Ph	C ₂₅ H ₃₁ NO ₇
256876	CH2CO2Et	2-MeO-Ph	C ₂₅ H ₃₁ NO ₆
256877	(CH2)6CO2Et	2-MeO-Ph	C ₃₀ H ₄₁ NO ₆
256878	CO2H	2-MeO-Ph	C ₂₂ H ₂₅ NO ₆

SOURCE – SS Pharm.

REFERENCES

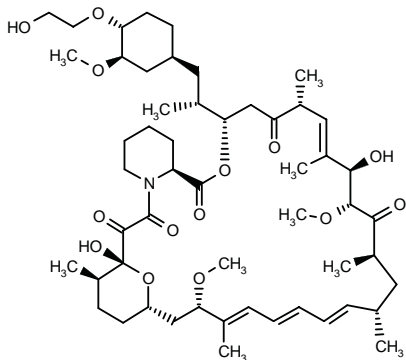
1. Hasegawa, H. et al. (SS Pharm. Co., Ltd.) *Novel pyridine derivs. and medicines containing the same as active ingredient*. WO 9733870.

SDZ-RAD*

210424

[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*R*)],15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-12-[2-[4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone

40-*O*-(2-Hydroxyethyl)rapamycin



C53-H83-N-O14; Mol wt: 958.24

ACTION – Immunosuppressant, a rapamycin derivative with high affinity for FKBP12 (IC₅₀ = 1.8-2.6 nM), proven to inhibit IL-6-stimulated proliferation of IL-6-dependent hybridoma clone B13-29-15 and fetal calf serum-stimulated proliferation of bovine vascular smooth muscle cells (VSMC; IC₅₀ = 0.2-1.4 and 0.9-3.6 nM, respectively). It demonstrated immunosuppressive activity in the murine mixed lymphocyte reaction (MLR) and against the proliferative response of antigen-specific human T-cell clones (IC₅₀ = 0.2-1.6 and 0.05-0.17 nM, respectively). The *in vitro* activity of SDZ-RAD was about 2-5 times lower than that of rapamycin. In rat models of localized graft-versus-host reaction, heart and kidney allograft rejection and mercuric choride-induced glomerulonephritis, the compound was effective at doses of 1-5 mg/kg/day p.o., with at least equivalent activity to rapamycin. It showed synergistic immunosuppression when used in combination with ciclosporin in rat kidney and heart allotransplantation models. Coadministration of single oral doses of the drug did not alter ciclosporin pharmacokinetics in renal transplant patients maintained on stable doses of Neoral(R), and no serious side effects were noted.

SOURCE – Novartis.

REFERENCES

1. Cottens, S. and Sedrani, R. (Sandoz-Erfindungen VmbH; Sandoz Patent GmbH; Sandoz, Ltd.) *O-Alkylated rapamycin derivs. and their use, particularly as immunosuppressants*. EP 663916, JP 96502266, US 5665772, WO 9409010.

2. Cottens, S. et al. (Sandoz, Ltd.; Sandoz-Patent GmbH; Sandoz-Erfindungen VmbH). *Pharmaceutical compsns*. WO 9613273.

3. Jackman, M. et al. (Sandoz, Ltd.; Sandoz-Patent GmbH; Sandoz-Erfindungen VmbH). *Pharmaceutical compsns*. WO 9613249.

4. Legay, F. and Wenger, R. (Sandoz, Ltd.; Sandoz-Patent GmbH; Sandoz-Erfindungen VmbH) *Assay kit*. WO 9507468.

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6. Schuler, W. et al. (Novartis AG) *Use of rapamycin derivs. in vasculopathies and xenotransplantation*. WO 9735575.

7. Appel, S. et al. *Safety, tolerability, and pharmacokinetics of the new immunosuppressant SDZ RAD in stable renal transplant recipients*. 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 359.

8. Schuler, W. et al. *SDZ RAD, a new rapamycin derivative*. Transplantation 1997, 64(1): 36.

9. Schuurman, H.-J. et al. *SDZ RAD, a new rapamycin derivative*. Transplantation 1997, 64(1): 32.

10. *The new immunosuppressant SDZ RAD: Pharmacological properties in vitro and in vivo*. Transplantation News (Novartis Newsletter) 1997.

11. Novartis Transplantation Company Brochure 1997, August.

*Identified compound **210424** Annu Drug Data Rep 1994, 16(9): 850.

WB-2663B

255507

ACTION – Immunosuppressant isolated from the culture of *Pseudomonas* sp. No. 2663 (FERM BP-3421), with antibacterial, antiinflammatory and liver-regenerating effects and low acute toxicity. It prolonged the survival of skin from mouse ear transplanted onto rat abdomen at a dose of 0.01 mg/kg/day x 14 days i.m.

SOURCE – Fujisawa.

REFERENCES

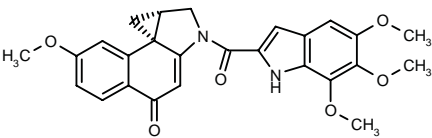
1. Isono, K. et al. (Fujisawa Pharm. Co., Ltd.) *Immunosuppressant including WB2663B substance*. JP 97221428.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

255660

(8*bR*,9*aS*)-7-Methoxy-2-(5,6,7-trimethoxy-1*H*-indol-2-ylcarbonyl)-2,4,9,9*a*-tetrahydro-1*H*-benzo[*e*]cycloprop[*c*]indol-4-one



C26-H24-N2-O6; Mol wt: 460.49

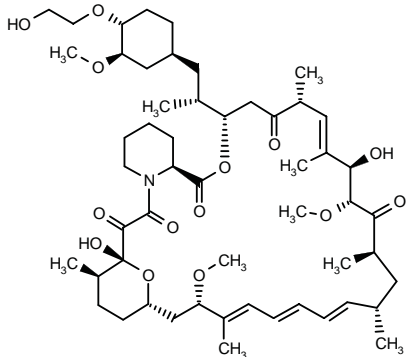
ACTION – Antineoplastic agent with DNA-alkylating activity, a duocarmycin analog containing a new alkylating subunit, 7-methoxy-1,2,9,9*a*-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (MCBI). Compound exhibited the same selectivity and efficiency of DNA alkylation as (+)-duocarmycin SA. Other related compounds containing the MCBI subunit are:

SDZ-RAD*

210424

[1*R*,9*S*,12*S*[(1''*R*,3''*R*,4''*R*)],15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-12-[2-[4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone

40-*O*-(2-Hydroxyethyl)rapamycin



C53-H83-N-O14; Mol wt: 958.24

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SOURCE – Novartis.

REFERENCES

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*Identified compound **210424** Annu Drug Data Rep 1994, 16(9): 850.

WB-2663B

255507

ACTION – Immunosuppressant isolated from the culture of *Pseudomonas* sp. No. 2663 (FERM BP-3421), with antibacterial, antiinflammatory and liver-regenerating effects and low acute toxicity. It prolonged the survival of skin from mouse ear transplanted onto rat abdomen at a dose of 0.01 mg/kg/day x 14 days i.m.

SOURCE – Fujisawa.

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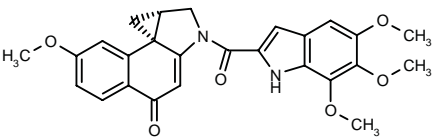
1. Isono, K. et al. (Fujisawa Pharm. Co., Ltd.) *Immunosuppressant including WB2663B substance*. JP 97221428.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

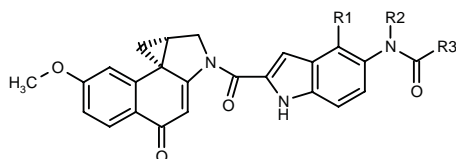
255660

(8*bR*,9*aS*)-7-Methoxy-2-(5,6,7-trimethoxy-1*H*-indol-2-ylcarbonyl)-2,4,9,9*a*-tetrahydro-1*H*-benzo[*e*]cycloprop[*c*]indol-4-one

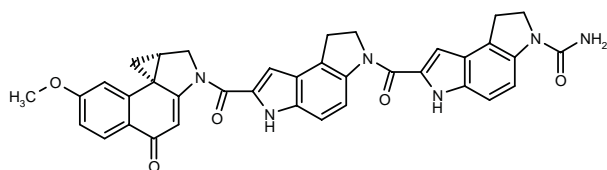


C26-H24-N2-O6; Mol wt: 460.49

ACTION – Antineoplastic agent with DNA-alkylating activity, a duocarmycin analog containing a new alkylating subunit, 7-methoxy-1,2,9,9*a*-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (MCBI). Compound exhibited the same selectivity and efficiency of DNA alkylation as (+)-duocarmycin SA. Other related compounds containing the MCBI subunit are:



Compound	R1	R2	R3	Formula
256845	H	H	2-indolyl	C ₃₂ H ₂₄ N ₄ O ₄
256846	-(CH ₂) ₂ -		NH ₂	C ₂₆ H ₂₂ N ₄ O ₄



256847: C37-H30-N6-O5

SOURCE – Scripps Res. Inst., La Jolla, CA (US).

REFERENCES

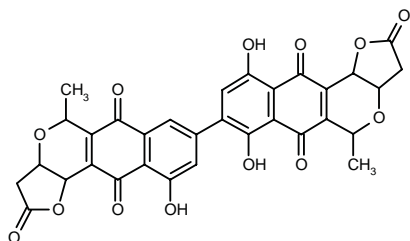
1. Boger, D.L. (The Scripps Res. Inst.) *MCBI analogs of CC-1065 and the duocarmycins*. WO 9732850.

ANTIBIOTICS AND ALKALOIDS

9-HYDROXYCRISAMICIN A

253746

8-(10-Hydroxy-5-methyl-2,6,11-trioxo-3,3a,5,6,11b-hexahydro-2H-furo[3,2-b]naphtho[2,3-d]pyran-8-yl)-7,10-dihydroxy-5-methyl-3,3a,5,6,11,11b-hexahydro-2H-furo[3,2-b]naphtho[2,3-d]pyran-2,6,11-trione



C32-H22-O13; Mol wt: 614.52

ACTION – Cytotoxic isochromanquinone antibiotic isolated from the culture of *Micromonospora* sp. SA246, with weak antimicrobial activity against Gram-positive bacteria (MIC = 6.25-25 µg/ml) and no activity against Gram-negative bacteria, yeast or fungi. In exhibited potent cytotoxic activity against human cancer cell lines such as ovarian SK-OV-3, colon HCT15, melanoma SK-MEL-2, lung A549 and CNS XF498 (ED₅₀ = 0.47-0.65 µg/ml).

SOURCE – Chungnam Natl. Univ., Taejon (KR); Korea Ginseng & Tobacco Res. Inst., Taejon (KR); Korea Res. Inst. Biosci. Biotechnol., Taejon (KR); Kyung Hee Univ., Kyungki-Do (KR); Mokwon Univ., Taejon (KR).

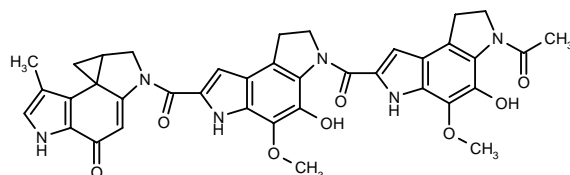
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QM16-A

255497

2-[6-(6-Acetyl-5-hydroxy-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-ylcarbonyl)-5-hydroxy-4-methoxy-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-ylcarbonyl]-7-methyl-1,2,4,5,8,8a-hexahydrocyclopropa[c]pyrrolo[3,2-e]indol-4-one



C38-H34-N6-O8; Mol wt: 702.72

ACTION – Antineoplastic agent produced by culturing the microorganism *Streptomyces* sp. QM16 (FERM BP-5363), with *in vitro* cytotoxicity against murine P388 leukemia, human leukemia K562, human epidermoid carcinoma A431 and human gastric cancer MKN28 cells (IC₅₀ = 0.08, 0.86, 0.72 and 0.75 ng/ml, respectively). *In vivo*, it prolonged survival time in mice bearing P388 leukemia (131% at 0.037 mg/kg/day i.p. on days 1, 5 and 9).

SOURCE – Kirin Brewery.

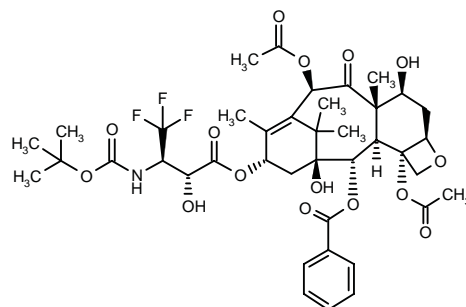
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ANTIMITOTIC DRUGS

255641

[2aR-[2αα,4β,4aβ,6β,9α(2R,3S),11β,12α,12αα,12bα]]-6,12b-Diacetoxy-12-benzoyloxy-9-[3-(*tert*-butoxycarbonylamino)-4,4,4-trifluoro-2-hydroxybutyryloxy]-4,11-dihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benz[1,2-b]oxet-5-one



C40-H50-F3-N-O15; Mol wt: 841.83

ACTION – Antineoplastic taxoid tested for activity against a variety of human tumor cell lines including ovarian carcinoma A121 (IC₅₀ = 0.37 nM), non-small cell lung carcinoma A549 (IC₅₀ = 0.25 nM), colon carcinoma HT-29 (IC₅₀ = 0.4 nM), and against drug-sensitive human breast cancer MCF-7 cells (IC₅₀ = 0.25 nM) and drug-resistant MCF-7 cells (IC₅₀ = 17 nM; IC₅₀ paclitaxel and docetaxel = 300 and 235 nM, respectively).

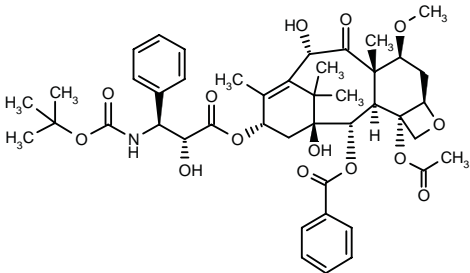
SOURCE – State Univ. New York, Stony Brook, NY (US).

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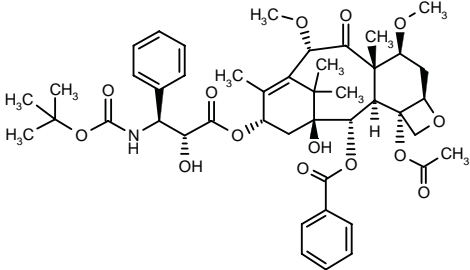
255672

[2a*R*-[2α,4β,4aβ,6α,9α(2*R*,3*S*),11β,12α,12aα,12bα]]-12b-Acetoxy-9-[3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropionyloxy]-12-benzoyloxy-6,11-dihydroxy-4-methoxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C44-H55-N-O14; Mol wt: 821.92

ACTION – Antineoplastic taxoid active against tumors that are resistant to paclitaxel and docetaxel. Reported to be active *in vivo* in mice bearing melanoma B16 at doses of 1-10 mg/kg i.p. Another specifically claimed taxoid is:



256539: C45-H57-N-O14

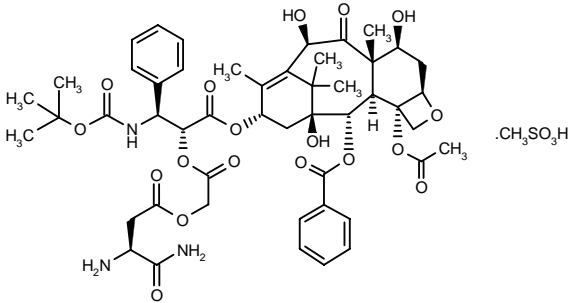
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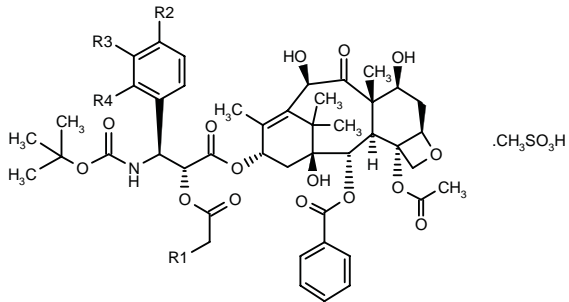
256438

[2a*R*-[2α,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12aα,12bα]]-12b-Acetoxy-9-[2-[2-(*L*-isoasparaginyloxy)acetoxy]-3-(*tert*-butoxycarbonylamino)-3-phenylpropionyloxy]-12-benzoyloxy-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one methanesulfonate



C49-H61-N3-O18.C-H4-O3-S; Mol wt: 1076.13

ACTION – Antineoplastic agent, a taxane derivative with improved water solubility compared to paclitaxel. Compound was shown to prolong survival in mice bearing B16 melanoma inoculated either s.c. (ILS = 198.3% at 6.3 mg/kg/day i.v. for 5 days) or i.p. (ILS = 129.2% at 12.5 mg/kg/day i.p. for 4 days). Other related compounds include the following:



Compound	R1	R2=R4	R3	Formula
257322	CH2CO2Et	H	H	C ₄₈ H ₆₁ NO ₁₇ .CH ₄ O ₃ S
257323	H-L-Pro-O	H	H	C ₅₀ H ₆₂ N ₂ O ₁₇ .CH ₄ O ₃ S
257324	(S)-(CH2)3OCO- CH2CH(NH2)CO2Et	H	H	C ₅₄ H ₇₀ N ₂ O ₁₉ .CH ₄ O ₃ S
257325	H-Ala-NHCH2	H	H	C ₄₉ H ₆₃ N ₃ O ₁₆ .CH ₄ O ₃ S
257326	(S)-OCOCH2CH(NH2)CO2Et	H	F	C ₅₁ H ₆₃ FN ₂ O ₁₉ .CH ₄ O ₃ S
257327	(S)-OCOCH2CH(NH2)- CO2CH2CH2OMe	F	H	C ₅₂ H ₆₄ F ₂ N ₂ O ₂₀ .CH ₄ O ₃ S

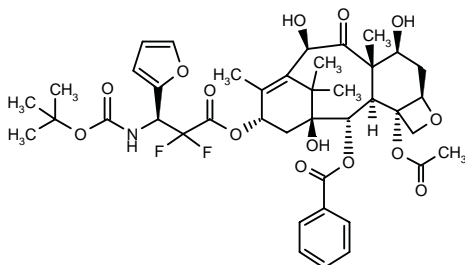
SOURCE – Tanabe Seiyaku.

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257453

[2a*R*,4*S*,4a*S*,6*R*,9*S*(3*S*),11*S*,12*S*,12a*R*,12b*S*]-3-*tert*-Butoxycarbonylamino-2,2-difluoro-3-(2-furyl)propanoic acid 12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca-[3,4]benz[1,2-*b*]oxet-9-yl ester



C41-H49-F2-N-O14; Mol wt: 817.83

M.p. 188-91 °C.

ACTION – Antineoplastic agent, an analog of docetaxel with cytotoxic activity and microtubule disassembly-inhibitory activity. *In vitro* cytotoxic activity was demonstrated against mouse leukemia P388 cells (GI_{50} = 5.21 ng/ml), human lung cancer PC-6, PC-12 and SBC-3 cells (GI_{50} = 1.43, 9.28 and 0.825 ng/ml, respectively) and doxorubicin-resistant SBC-3 cells (GI_{50} = 53.3 ng/ml). Microtubule disassembly assays demonstrated comparable activity to docetaxel.

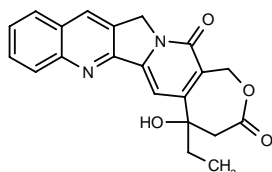
SOURCE – Daiichi Pharm.

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DNA-INTERCALATING DRUGS**BN-80245*****247645**

(±)-5-Ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione



C21-H18-N2-O4; Mol wt: 362.38

ACTION – Antineoplastic agent, a derivative of camptothecin with topoisomerase I-inhibitory activity comparable to camptothecin (40 ± 9% vs. 36 ± 6% inhibition at 100 μM) and more potent cytotoxic activity against murine leukemia L1210 cells (IC_{50} = 16.2 nM). The compound is more stable than camptothecin.

SOURCES – Beaufour-Ipsen; Lab. Lasa; SCRAS.

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*Identified compound **247645** Annu Drug Data Rep 1997, 19(6): 555.

HORMONAL AGENTS**GROWTH INHIBITORY PEPTIDE****255194**

Leucyl-seryl-glutamyl-aspartyl-lysyl-leucyl-leucyl-alanyl-cysteinyl-glycyl-glutamyl-glycyl-alanyl-alanyl-aspartyl-isoleucyl-isoleucyl-isoleucyl-glycyl-histidyl-leucyl-cysteinyl-isoleucyl-arginyl-histidyl-glutamyl-methionyl-threonyl-prolyl-valyl-asparaginyl-prolyl-glycyl-valine

GIP

C154-H255-N43-O48-S3; Mol wt: 3573.15

ACTION – Non-naturally occurring peptide capable of inhibiting cell growth stimulated by growth factors whose receptors are members of the steroid/thyroid hormone/vitamin receptor superfamily, especially steroid-stimulated growth such as by estrogen. The peptide inhibited estrogen-stimulated growth of mouse uterus by 33-79% when injected i.p. into immature female mice at doses of 25-100 ng/mouse, and it inhibited human breast adenocarcinoma MCF-7 cell growth by up to 74% at concentrations of 0.1 pM-0.1 nM. It also inhibited hydrocortisone-induced mouse spleen growth by 100% at a dose of 1.0 μg/mouse and human chorionic gonadotropin (hCG)-stimulated growth of mouse ovary by 100% at 1 μg/mouse.

SOURCE – Health Research.

REFERENCES

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CANCER IMMUNOTHERAPY**RITUXIMAB**

Prop INN

204337

Immunoglobulin G₁ (human-mouse monoclonal IDEC-C2B8 γ₁-chain antihuman antigen CD20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer

IDEC-C2B8*

ACTION – Genetically engineered pan-B anti-CD20 monoclonal antibody that contains both human and murine components (chimeric)*.

INDICATION – Treatment of non-Hodgkin's lymphoma.

PRESENTATION – Vials, 10 and 50 ml containing 100 and 500 mg of rituximab, respectively.

PROPRIETARY NAMES – *MabThera* (CH); *Rituxan* (US).

SOURCES – Discovered by IDEC and jointly developed with Genentech, Roche and Zenyaku Kogyo; copromoted in the U.S. by IDEC and Genentech and marketed outside the U.S. and Japan by Roche.

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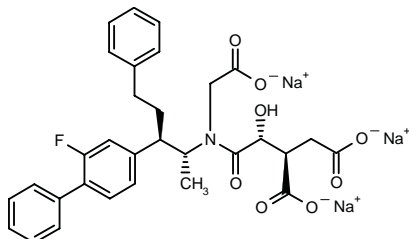
*The anti-CD20 antibody technology was licensed to IDEC and Genentech by XOMA.

*Annu Drug Data Rep 1994, 16(4): 398.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

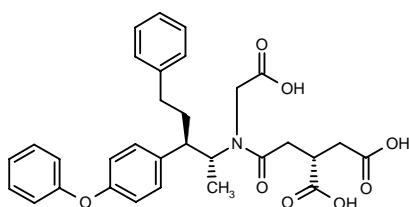
254996

2(*R*)-[2-[*N*-(Carboxymethyl)-*N*-[2(*R*)-(2-fluorobiphenyl-4-yl)-1(*R*)-methyl-4-phenylbutylamino]-1(*R*)-hydroxy-2-oxoethyl]succinic acid trisodium salt



C31-H29-F-N-Na3-O8; Mol wt: 631.54

ACTION – Antineoplastic agent that acts by inhibiting protein farnesyltransferase (IC_{50} = 0.1 nM using rat brain preparations) and the farnesylation of the oncogene protein Ras (IC_{50} = 1.3 μ M in NIH3T3 cells transfected with activated *ras* gene). Another compound from this series of substituted amide derivatives is:



257833: C31-H33-N-O8

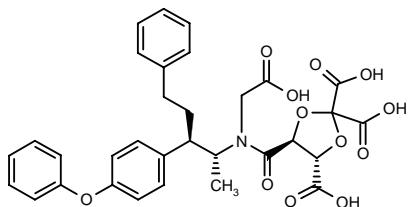
SOURCE – Banyu.

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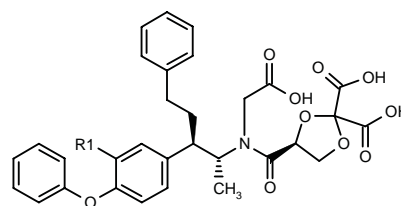
254997

5(*S*)-[*N*-(Carboxymethyl)-*N*-[1(*R*)-methyl-2(*R*)-(4-phenoxyphenyl)-4-phenylbutyl]carbamoyl]-1,3-dioxolane-2,2,4(*S*)-tricarboxylic acid

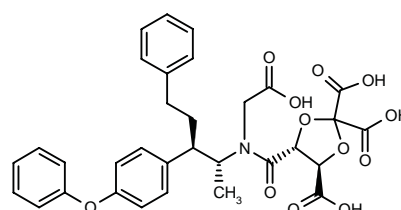


C32-H31-N-O12; Mol wt: 621.60

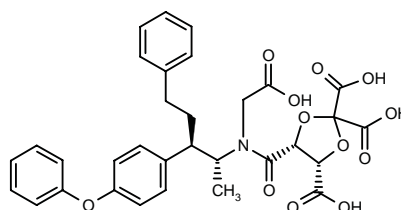
ACTION – Antineoplastic agent, a potent inhibitor of protein farnesyltransferase (IC_{50} = 0.095 nM in rat brain preparations) and of Ras farnesylation (IC_{50} = 1.9 μ M in NIH3T3 cells transduced with activated *ras* gene). *In vivo*, it inhibited the growth of *ras*-transduced NIH3T3 tumors in nude mice (75, 92 and 99% inhibition at 10, 20 and 40 mg/kg s.c., respectively). A representative compound from a series of 1,3-dioxolane derivatives, wherein the following are also included:



Compound	R1	Formula
257822	H	C ₃₁ H ₃₁ NO ₁₀
257825	OMe	C ₃₂ H ₃₃ NO ₁₁
257826	OH	C ₃₁ H ₃₁ NO ₁₁



257823: C32-H31-N-O12



257824: C32-H31-N-O12

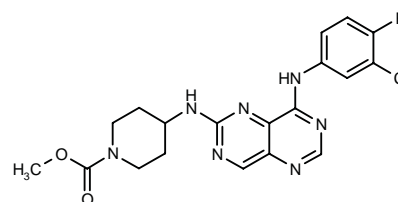
SOURCE – Banyu.

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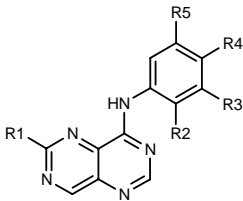
255678

4-[8-(3-Chloro-4-fluorophenylamino)pyrimido[5,4-*d*]pyrimidin-2-ylamino]piperidine-1-carboxylic acid methyl ester



C19-H19-Cl-F-N7-O2; Mol wt: 431.86

ACTION – Antineoplastic agent that acts by inhibiting tyrosine kinase-dependent signal transduction, particularly epidermal growth factor (EGF) receptor-mediated signal transduction. It inhibited EGF-stimulated proliferation of F/L-HERc cells with an IC_{50} value of 3 nM, while showing an IC_{50} > 10 μ M for inhibition of IL-3-stimulated cell proliferation. Other compounds from this series of specifically claimed pyrimido[5,4-*d*]pyrimidines include the following:



Compound	R1	R2	R3	R4	R5	Formula
256640	4-(NH2CH2)-1-Pip	H	Cl	F	H	C ₁₈ H ₁₉ ClFN ₇
256641	trans-4-(4-morpholinyl-CO)-cyclohexyl-NH	H	Cl	NH2	Cl	C ₂₃ H ₂₆ Cl ₂ N ₈ O ₂
256642	4-Pip-CH2NH	H	Cl	F	H	C ₁₈ H ₁₉ ClFN ₇
256643	4-(4-Me-1-Piz)-cyclohexyl-NH	H	Cl	F	H	C ₂₃ H ₂₆ ClFN ₈
256644	trans-4-OH-cyclohexyl-NH	Cl	H	NH2	Cl	C ₁₈ H ₁₉ Cl ₂ N ₇ O

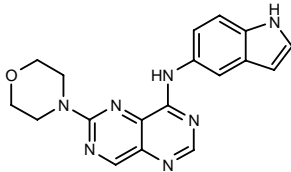
SOURCE – Boehringer Ingelheim.

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1. Himmelsbach, F. et al. (Dr. Karl Thomae GmbH) *Pyrimido[5,4-d]pyrimidines, medicaments containing these cpds., their use and process for their production.* DE 19608588, WO 9732880.

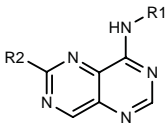
255680

8-(1*H*-Indol-5-ylamino)-2-(4-morpholinyl)pyrimido[5,4-*d*]-pyrimidine



C18-H17-N7-O; Mol wt: 347.38

ACTION – Antineoplastic agent that acts by inhibiting tyrosine kinase-dependent signal transduction, particularly epidermal growth factor (EGF) receptor-mediated signal transduction. It inhibited EGF-induced proliferation in F/L-HERc cells with an IC₅₀ value of 21 nM, while showing an IC₅₀ value of 10 μM for inhibition of IL-3-mediated cell proliferation. A representative compound from a series of specifically claimed pyrimido[5,4-*d*]pyrimidines, wherein the following are also included:



Compound	R1	R2	Formula
256633	5-indolyl	trans-4-OH-cyclohexyl-NH	C ₂₀ H ₂₁ N ₇ O
256634	3-Cl-4-F-Ph	4-(4-morpholinyl-COCH2)-1-Piz	C ₂₂ H ₂₄ ClFN ₈ O ₂
256635	3-Cl-4-F-Ph	4-morpholinyl-NH	C ₁₆ H ₁₅ ClFN ₇ O
256636	3-Cl-4-F-Ph	4-Pyr-CH2NH	C ₁₈ H ₁₃ ClFN ₇
256637	3-Cl-4-F-Ph	1-(CF3CO)-4-Pip-NH	C ₁₉ H ₁₆ ClF ₄ N ₇ O

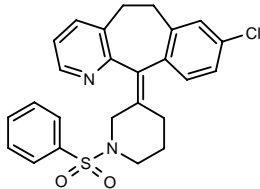
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Himmelsbach, F. et al. (Dr. Karl Thomae GmbH) *Pyrimido[5,4-d]pyrimidines, medicaments containing these cpds., their use and process for their production.* DE 19608653, WO 9732882.

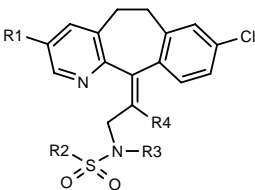
256300

(*Z*)-8-Chloro-11-[1-(phenylsulfonyl)piperidin-3-ylidene]-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine



C25-H23-Cl-N2-O2-S; Mol wt: 450.98

ACTION – Antineoplastic agent, a selective protein farnesyltransferase inhibitor (IC₅₀ = 0.71 μM). Compound inhibited the growth of Ras-transformed tumor cells (IC₅₀ < 3.1 μM) without displaying cytotoxic activity against normal cells (IC₅₀ > 50 μM). Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
257979	Br	Ph	-(CH2)3-		C ₂₈ H ₂₂ BrClN ₂ O ₂ S
257980	H	Ph	-(CH2)2-		C ₂₄ H ₂₁ ClN ₂ O ₂ S
257981	H	4-F-Ph	-(CH2)3-		C ₂₆ H ₂₂ ClFN ₂ O ₂ S
257982	H	2-thienyl	-(CH2)3-		C ₂₃ H ₂₁ ClN ₂ O ₂ S ₂

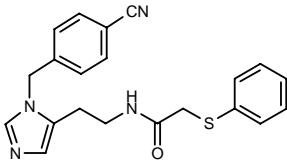
SOURCE – Schering-Plough.

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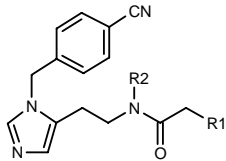
257137

N-[2-[1-(4-Cyanobenzyl)imidazol-5-yl]ethyl]-2-(phenylsulfonyl)acetamide



C21-H20-N4-O-S; Mol wt: 376.48

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	Formula
257598	OPh	H	C ₂₁ H ₂₀ N ₄ O ₂
257599	NHCH ₂ Ph	H	C ₂₂ H ₂₃ N ₅ O
257600	SOPh	Me	C ₂₂ H ₂₂ N ₄ O ₂ S
257601	3,5-(Cl)2-PhNH	Me	C ₂₂ H ₂₁ Cl ₂ N ₅ O
257602	CH ₂ NHCH ₂ CH(Ph) ₂	Me	C ₃₁ H ₃₃ N ₅ O
257603	N(Me)CH ₂ Ph	H	C ₂₃ H ₂₅ N ₅ O
257604	N(Me)CH ₂ Ph	Me	C ₂₄ H ₂₇ N ₅ O
257605	CH(CH ₂ CH ₂ Ph)N(Me)CH ₂ Ph	Me	C ₃₃ H ₃₇ N ₅ O

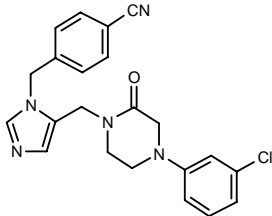
SOURCE – Merck & Co.

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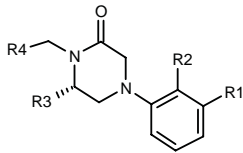
257140

4-[5-[4-(3-Chlorophenyl)-2-oxopiperazin-1-ylmethyl]imidazol-1-ylmethyl]benzonitrile



C₂₂-H₂₀-Cl-N₅-O; Mol wt: 405.89

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed peptidomimetic ketopiperazine-containing compounds include the following:



Compound	R1	R2	R3	R4	Formula
258953	Me	Me	Bu	1-(4-CN-PhCH ₂)-5-imidazolyl	C ₂₈ H ₃₃ N ₅ O
258954	Cl	H	H	3-(4-CN-PhCH ₂)-4-Pyr	C ₂₄ H ₂₁ ClN ₄ O

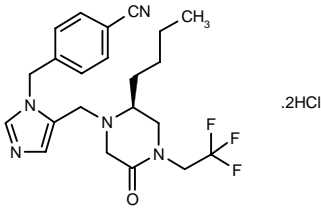
SOURCE – Merck & Co.

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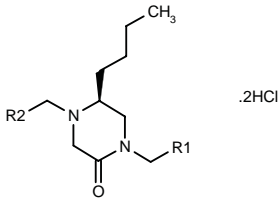
257142

4-[5-[2(S)-Butyl-5-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-ylmethyl]imidazol-1-ylmethyl]benzonitrile dihydrochloride



C₂₂-H₂₆-F₃-N₅-O.2HCl; Mol wt: 506.40

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed peptidomimetic piperazine- or piperazinone-containing compounds include the following:



Compound	R1	R2	Formula
258955	CH ₂ CF ₃	1-(4-CN-PhCH ₂)-5-imidazolyl	C ₂₃ H ₂₈ F ₃ N ₅ O.2HCl
258956	cyclopropyl	1-(4-CN-PhCH ₂)-5-imidazolyl	C ₂₄ H ₃₁ N ₅ O.2HCl
258957	CF ₃	3-(4-CN-PhCH ₂)-4-Pyr	C ₂₄ H ₂₇ F ₃ N ₄ O.2HCl

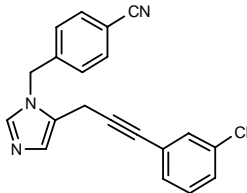
SOURCE – Merck & Co.

REFERENCES

1. Wei, D.D. and Williams, T.M. (Merck & Co.) *Inhibitors of farnesyl-protein transferase*. WO 9736593.

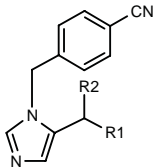
257161

4-[5-[3-(3-Chlorophenyl)-2-propynyl]imidazol-1-ylmethyl]benzonitrile

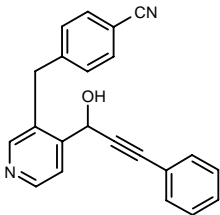


C₂₀-H₁₄-Cl-N₃; Mol wt: 331.80

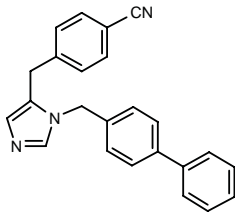
ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of Ras farnesylation. Also claimed for the treatment of blindness related to retinal vascularization, benign proliferative disorders, hepatitis delta and related viral infections and polycystic kidney disease, as well as for preventing restenosis. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
257851	CH=CHPh	H	C ₂₀ H ₁₇ N ₃
257852	3-Cl-PhCH ₂ CH ₂	OH	C ₂₀ H ₁₈ ClN ₃ O
257853	CH ₂ -ethynylene-Ph	OH	C ₂₁ H ₁₇ N ₃ O
257856	4-Ph-Ph	OH	C ₂₄ H ₁₉ N ₃ O



257854: C22-H16-N2-O



257855: C24-H19-N3

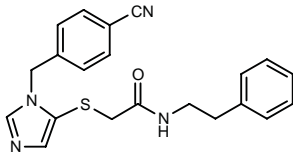
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736876.

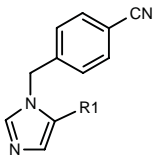
257162

2-[1-(4-Cyanobenzyl)imidazol-5-ylsulfanyl]-N-(2-phenylethyl)acetamide



C21-H20-N4-O-S; Mol wt: 376.48

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of Ras farnesylation. Also claimed for the treatment of blindness related to retinal vascularization, benign proliferative disorders, hepatitis delta and related viral infections and polycystic kidney disease, as well as for preventing restenosis. Other specifically claimed compounds include the following:



Compound	R1	Formula
257879	SCH ₂ CONHCH ₂ Ph	C ₂₀ H ₁₈ N ₄ OS
257880	CH ₂ SCH ₂ CH ₂ NHCOPh	C ₂₁ H ₂₀ N ₄ OS
257881	NHCH ₂ CONHCH ₂ CH ₂ Ph	C ₂₁ H ₂₁ N ₅ O
257882	3-Cl-PhCH ₂ NHCOCH ₂ OCH ₂	C ₂₁ H ₁₉ ClN ₄ O ₂
257883	3-Cl-PhNHCOCH ₂ NHCH ₂ CH ₂	C ₂₁ H ₂₀ ClN ₅ O

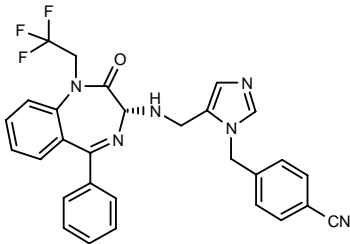
SOURCE – Merck & Co.

REFERENCES

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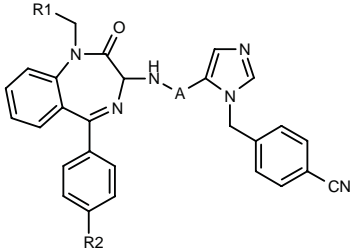
257163

4-[5-[2-Oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-1,4-benzodiazepin-3(R)-ylaminomethyl]imidazol-1-ylmethyl]benzonitrile



C29-H23-F3-N6-O; Mol wt: 528.54

ACTION – Antineoplastic agent, a non-thiol-containing inhibitor of protein farnesyltransferase and of Ras farnesylation expected to have an improved pharmacokinetic profile and less systemic toxicity than other inhibitors containing a thiol moiety. Also claimed for the treatment of blindness related to retinal vascularization, benign proliferative disorders, hepatitis delta and related viral infections and polycystic kidney disease, as well as for preventing restenosis. Other specifically claimed peptidomimetic benzodiazepine-containing compounds include the following:



Compound	R1	R2	A	Isomer	Formula
258146	CF ₃	H	CH ₂	S	C ₂₉ H ₂₃ F ₃ N ₆ O
258147	CF ₃	H	COCH ₂	R	C ₃₀ H ₂₃ F ₃ N ₆ O ₂
258148	CF ₃	H	COCH ₂	S	C ₃₀ H ₂₃ F ₃ N ₆ O ₂
258149	4-MeO-Ph	H	COCH ₂	RS	C ₃₆ H ₃₀ N ₆ O ₃
258150	H	H	COCH ₂	R	C ₂₉ H ₂₄ N ₆ O ₂
258151	CF ₃	F	COCH ₂	R	C ₃₀ H ₂₂ F ₄ N ₆ O ₂
258152	CF ₃	H	CH ₂ CH ₂	R	C ₃₀ H ₂₅ F ₃ N ₆ O
258153	CF ₃	H	CH ₂ CH ₂	S	C ₃₀ H ₂₅ F ₃ N ₆ O

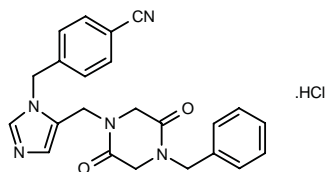
SOURCE – Merck & Co.

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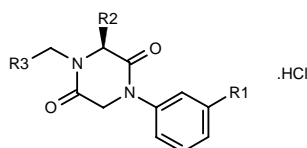
257169

4-[5-(4-Benzyl-2,5-dioxopiperazin-1-ylmethyl)imidazol-1-ylmethyl]benzonitrile hydrochloride



C23-H21-N5-O2.HCl; Mol wt: 435.91

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of Ras farnesylation. Also claimed for the treatment of blindness related to retinal vascularization, benign proliferative disorders, hepatitis delta and related viral infections and polycystic kidney disease, as well as for preventing restenosis. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
257918	Cl	H	1-(4-CN-PhCH2)-5-imidazolyl	C ₂₂ H ₁₈ ClN ₅ O ₂ .HCl
257919	Cl	Bu	1-(4-CN-PhCH2)-5-imidazolyl	C ₂₆ H ₂₆ ClN ₅ O ₂ .HCl
257920	Cl	H	3-(4-CN-PhCH2)-4-Pyr	C ₂₄ H ₁₉ ClN ₄ O ₂ .HCl
257921	H	H	1-(4-CN-PhCH2)-5-imidazolyl	C ₂₂ H ₁₉ N ₅ O ₂ .HCl

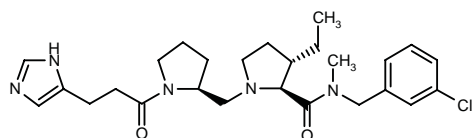
SOURCE – Merck & Co.

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257172

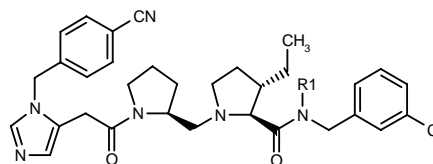
N-(3-Chlorobenzyl)-3(*S*)-ethyl-1-[1-[3-(1*H*-imidazol-5-yl)propionyl]pyrrolidin-2(*S*)-ylmethyl]-*N*-methyl-L-prolinamide



C26-H36-Cl-N5-O2; Mol wt: 486.06

ACTION – Antineoplastic agent that acts by inhibiting protein farnesyltransferase (IC₅₀ < 10 μM against human enzyme) and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced systemic toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis following percutaneous transluminal coronary angioplasty (PTCA) and for

the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Other specifically claimed imidazole-containing compounds include the following:



Compound	R1	Formula
257912	H	C ₃₂ H ₃₇ ClN ₆ O ₂
257913	Me	C ₃₃ H ₃₉ ClN ₆ O ₂

SOURCE – Merck & Co.

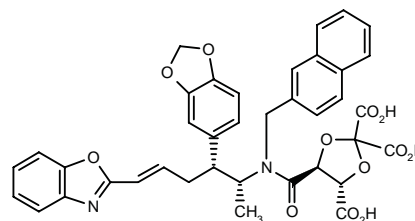
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J-104134*

252912

5(*S*)-[*N*-[2(*R*)-(1,3-Benzodioxol-5-yl)-5-(2-benzoxazolyl)-1(*R*)-methyl-4(*E*)-pentenyl]-*N*-(2-naphthylmethyl)carbamoyl]-1,3-dioxolane-2,2,4(*S*)-tricarboxylic acid



C38-H32-N2-O12; Mol wt: 708.68

ACTION – Antineoplastic agent, a potent farnesyl biphosphate (FPP)-based inhibitor of protein farnesyltransferase (IC₅₀ = 0.10 nM against enzyme from rat brain) and Ras protein farnesylation in *H-ras*-transformed NIH3T3 cells (IC₅₀ = 4.3 μM). It is the first FPP-competitive inhibitor to suppress tumor growth, as demonstrated in nude mice transplanted with *H-ras*-transformed NIH3T3 cells.

SOURCE – Banyu.

REFERENCES

1. Iwasawa, Y. et al. (Banyu Pharm. Co., Ltd.) *Cyclic amic acid derivs*. WO 9717321.

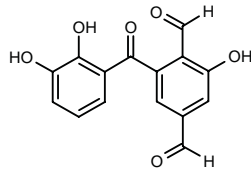
2. Aoyama, T. et al. *Development and synthesis of highly potent farnesylproteintransferase inhibitors and their structure-activity relationships*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-14.

*Identified compound **252912** (see **252065**) Annu Drug Data Rep 1997, 19(9): 840.

SCH-207278

256071

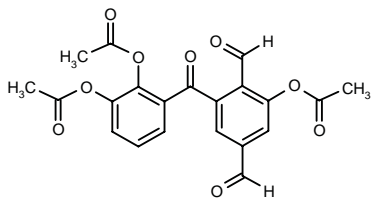
2-(2,3-Dihydroxybenzoyl)-6-hydroxyterephthalaldehyde



C15-H10-O6; Mol wt: 286.24

White powder, m.p. 201-3 °C (decomp.).

ACTION – Antineoplastic agent isolated from an unidentified fungus, an inhibitor of protein farnesyltransferase (IC₅₀ = 3.5 μM against recombinant human enzyme) with 20-fold selectivity over protein geranylgeranyltransferase-1 (IC₅₀ = 70 μM). Its triacetate (**256660**) displays a similar profile.



256660: C21-H16-O9

SOURCE – Schering-Plough.

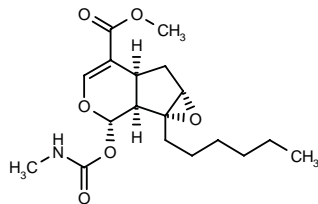
REFERENCES

1. Chu, M. et al. *Sch 207278: A novel farnesyl protein transferase inhibitor from an unidentified fungus*. *Bioorg Med Chem Lett* 1997, 7(19): 2547.

ANTIANGIOGENIC AGENTS

255671

[1a*R*-(1α,1β,2β,5α,6α)]-1a-Hexyl-2-(*N*-methylcarmoyloxy)-1a,1b,2,5a,6,6a-hexahydrooxireno[4,5]-cyclopenta[1,2-*c*]pyran-5-carboxylic acid methyl ester



C18-H27-N-O6; Mol wt: 353.41

ACTION – Antiangiogenic agent shown to inhibit cell migration and neovascularization in human umbilical vein endothelial cells (HUVEC) at 1 μg/ml. Other compounds from this series of iridoid derivatives include the following:



Compound	R1	R2	Formula
257818	ONa	Me	C ₁₂ H ₁₄ NNaO ₆
257819	OPh	Me	C ₁₈ H ₁₈ NO ₆
257820	4-(CH ₂ CH ₂ OH)-1-Piz	Me	C ₁₈ H ₂₇ N ₃ O ₆
257821	OMe	CH ₂ OCO ₂ NHMe	C ₁₅ H ₂₀ N ₂ O ₈

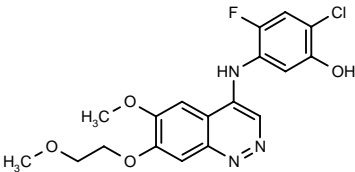
SOURCE – Tsumura.

REFERENCES

1. Morishige, H. et al. (Tsumura & Co.) *Novel iridoid derivs. and neovascularization inhibitors containing the same as active ingredient*. WO 9732868.

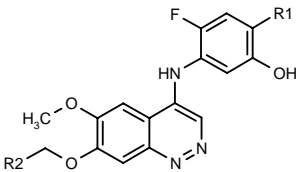
256153

4-(4-Chloro-2-fluoro-5-hydroxyphenylamino)-6-methoxy-7-(2-methoxyethoxy)cinnoline



C18-H17-Cl-F-N3-O4; Mol wt: 393.80

ACTION – Agent for the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, rheumatoid arthritis, diabetes, psoriasis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation and ocular diseases with retinal vessel proliferation, an inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase with significantly lower activity against epidermal growth factor (EGF) or fibroblast growth factor (FGF) R1 receptor tyrosine kinases. Within this series of specifically claimed cinnoline derivatives, the following are also included:



Compound	R1	R2	Formula
257359	Br	CH ₂ OMe	C ₁₈ H ₁₇ BrFN ₃ O ₄
257360	Me	CH ₂ OMe	C ₁₉ H ₂₀ FN ₃ O ₄
257361	Me	4-morpholinyl-CH ₂ CH ₂	C ₂₃ H ₂₇ FN ₄ O ₄
257362	Me	2-Me-4-thiazolyl	C ₂₁ H ₁₉ FN ₄ O ₃ S
257363	Me	1-pyrrolidinyl-CH ₂ CH ₂	C ₂₃ H ₂₇ FN ₄ O ₃

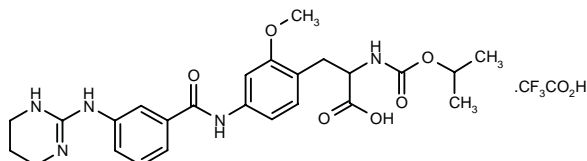
SOURCE – Zeneca.

REFERENCES

1. Thomas, A.P. and Hennequin, L.F.A. (Zeneca, Ltd.; Zeneca Pharma SA) *Cinnoline derivs. and use as medicine*. WO 9734876.

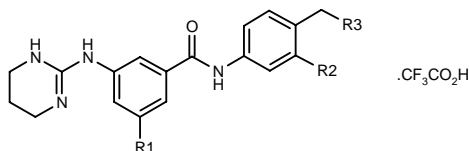
257148

N-(Isopropoxycarbonyl)-2-methoxy-4-[3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)benzamido]-DL-phenylalanine tri-fluoroacetate



C25-H31-N5-O6.C2-H-F3-O2; Mol wt: 611.57

ACTION – Agent for the treatment of cancer, tumor metastasis, angiogenesis, osteoporosis and restenosis, a vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist (IC_{50} = 0.2 nM) with much lower affinity for the fibrinogen (gpIIb/IIIa) receptor (IC_{50} = 1000 nM). Other specifically claimed compounds from this series of *para*-substituted phenylpropanoic acid derivatives include the following:



Compound	R1	R2	R3	Formula
257857	CF3	H	i-BuCONH(CO2H)	C ₂₆ H ₃₀ F ₃ N ₅ O ₄ .C ₂ HF ₃ O ₂
257858	H	OMe	CH2CO2H	C ₂₁ H ₂₄ N ₄ O ₄ .C ₂ HF ₃ O ₂

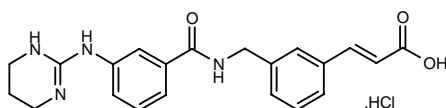
SOURCE – Searle.

REFERENCES

1. Chen, B.B. et al. (G.D. Searle & Co.) *Para-substd. phenylpropanoic acid derivs. as integrin antagonists*. WO 9736859.

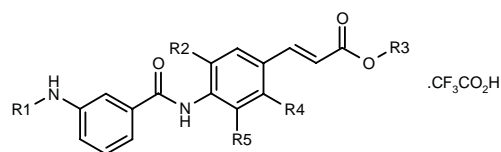
257149

3-[3-[3-(1,4,5,6-Tetrahydropyrimidin-2-ylamino)benzamido]methyl]phenyl]-2-propenoic acid hydrochloride

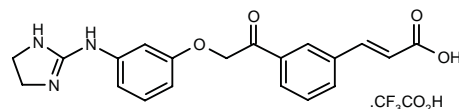


C21-H22-N4-O3.HCl; Mol wt: 414.89

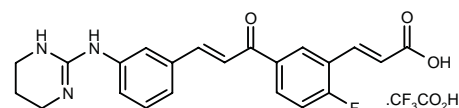
ACTION – Agent for the treatment of cancer, tumor metastasis, angiogenesis, osteoporosis and restenosis, a selective vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist (IC_{50} = 2.04 nM) with much lower affinity for the fibrinogen (gpIIb/IIIa) receptor (IC_{50} = 23,300 nM). Other specifically claimed compounds from this series of cinnamic acid derivatives include the following:



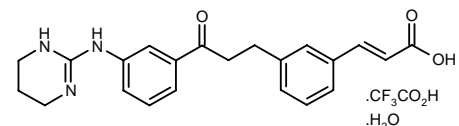
Compound	R1	R2	R3	R4	R5	Formula
257702	CONH2	Me	H	H	Me	C ₁₉ H ₁₉ N ₃ O ₄ .C ₂ HF ₃ O ₂
257703	3,4,5,6-tetrahydro-2-pyrimidinyl	H	Me	CO2H	H	C ₂₂ H ₂₂ N ₄ O ₅ .C ₂ HF ₃ O ₂
257704	5,6-dihydro-4H-1,3-thiazin-2-yl	Me	H	H	Me	C ₂₂ H ₂₃ N ₃ O ₃ S.C ₂ HF ₃ O ₂



257705: C20-H19-N3-O4.C2-H-F3-O2



257706: C22-H20-F-N3-O3.C2-H-F3-O2



257707: C22-H23-N3-O3.C2-H-F3-O2.H2O

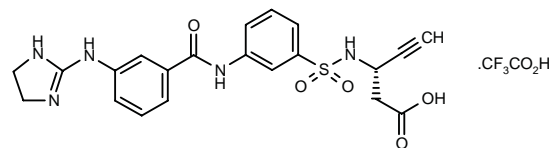
SOURCE – Searle.

REFERENCES

1. Chen, B.B. et al. (G.D. Searle & Co.) *Cinnamic acid derivs. and their use as integrin antagonists*. WO 9736860.

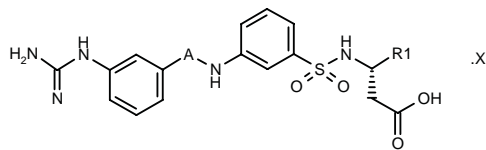
257150

3(S)-[3-[3-(4,5-Dihydro-1H-imidazol-2-ylamino)benzamido]phenylsulfonamido]-4-pentynoic acid trifluoroacetate



C21-H21-N5-O5-S.C2-H-F3-O2; Mol wt: 631.60

ACTION – Nonpeptide vitronectin ($\alpha_v\beta_3$) receptor antagonist (IC_{50} = 15.0 nM) with good selectivity relative to the fibrinogen (gpIIb/IIIa) receptor (IC_{50} = 418 nM), potentially useful in the treatment of tumor metastasis, osteoporosis, angiogenesis, retinopathy, inflammation, psoriasis and restenosis, as well as for use as an antiviral, antifungal and antimicrobial agent. A representative compound from a series of specifically claimed *meta*-substituted phenylsulfonamide derivatives, wherein the following are also included:



Compound	R1	A	X	Formula
257872	Ph	CO	CF3CO2H	C ₂₃ H ₂₃ N ₅ O ₅ S.C ₂ HF ₃ O ₂
257873	ethynyl	CO		C ₁₉ H ₁₉ N ₅ O ₅ S
257874	vinyl	CO	CF3CO2H	C ₁₉ H ₂₁ N ₅ O ₅ S.C ₂ HF ₃ O ₂
257875	3,5-(Cl)2-Ph	CO	CF3CO2H	C ₂₃ H ₂₁ Cl ₂ N ₅ O ₅ S.C ₂ HF ₃ O ₂
257876	3-Pyr	CO	3CF3CO2H	C ₂₂ H ₂₂ N ₆ O ₅ S.3C ₂ HF ₃ O ₂
257877	Ph	SO2	CF3CO2H	C ₂₂ H ₂₃ N ₅ O ₆ S ₂ .C ₂ HF ₃ O ₂
257878	ethynyl	CO	CF3CO2H	C ₁₉ H ₁₉ N ₅ O ₅ S.C ₂ HF ₃ O ₂

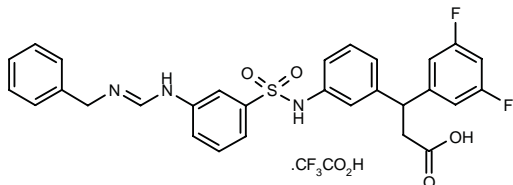
SOURCE – Searle.

REFERENCES

1. Chandrakumar, N. et al. (G.D. Searle & Co.) *Meta-substd. phenylene sulphonamide derivs.* WO 9736861.

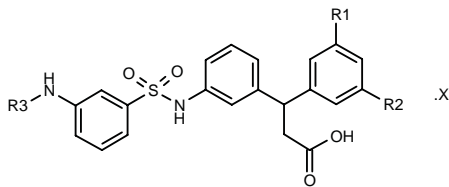
257151

3-[3-[3-(Benzyliminomethylamino)phenylsulfonamido]-phenyl]-3-(3,5-difluorophenyl)propionic acid trifluoroacetate

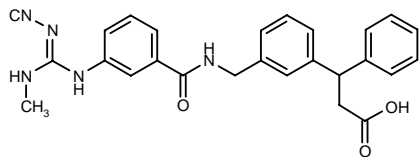


C29-H25-F2-N3-O4-S.C2-H-F3-O2; Mol wt: 663.61

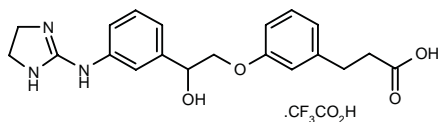
ACTION – Agent for the treatment of cancer, tumor metastasis, angiogenesis, osteoporosis and restenosis, a selective vitronectin ($\alpha_v\beta_3$ integrin) receptor antagonist (IC_{50} = 82.0 nM) with much lower affinity for the fibrinogen (gpIIb/IIIa) receptor (IC_{50} = 13,800 nM). Other specifically claimed compounds from this series of *meta*-substituted phenylene derivatives include the following:



Compound	R1=R2	R3	X	Formula
257868	H	CONHCH2Ph	H2O	C ₂₉ H ₂₇ N ₃ O ₅ S.H ₂ O
257871	Cl	C(NH2)=NCONH2	CF3CO2H	C ₂₃ H ₂₁ Cl ₂ N ₅ O ₅ S.C ₂ HF ₃ O ₂



257869: C26-H25-N5-O3



257870: C20-H23-N3-O4.C2-H-F3-O2

SOURCE – Searle.

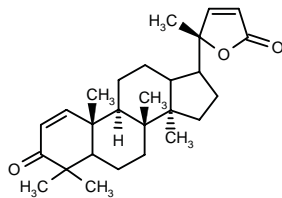
REFERENCES

1. Chandrakumar, N. et al. (G.D. Searle & Co.) *Meta-substd. phenylene derivs. and their use as $\alpha_v\beta_3$ integrin antagonists or inhibitors.* WO 9736862.

MISCELLANEOUS ANTINEOPLASTIC AGENTS

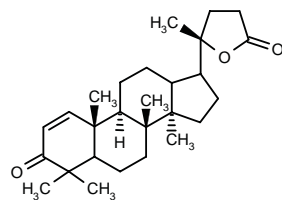
255515

5(*R*)-Methyl-5-(4,4,8 β ,14 α -tetramethyl-3-oxo-18-nor-1-androsten-17-yl)furan-2(5*H*)-one



C27-H38-O3; Mol wt: 410.60

ACTION – Antineoplastic agent isolated from the Egyptian plant *Cleome africana*, with *in vitro* cytotoxicity against murine P388 leukemia (IC_{50} = 1.9 μ g/ml). Another related steroid is:



257276: C27-H40-O3

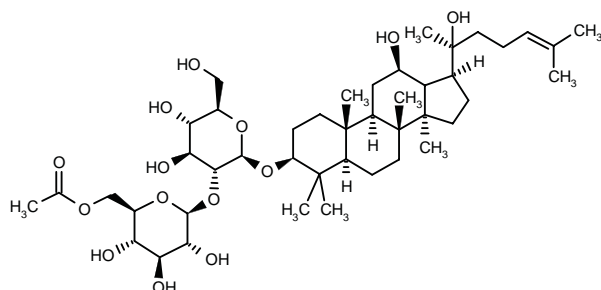
SOURCE – Katakura.

REFERENCES

1. Nagaya, H. et al. (Katakura Co., Ltd.) *Novel steroids.* JP 97221496.

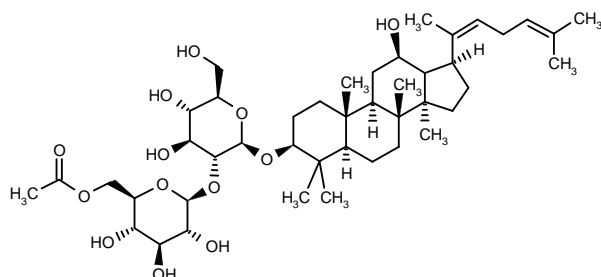
255628

3β-[2-*O*-(6-*O*-Acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyloxy]-18-nor-4,4,8β,14α-tetramethyl-5α-cholest-24-ene-12β,20-diol



C44-H74-O14; Mol wt: 827.06

ACTION – Antineoplastic agent proven to significantly inhibit the growth of human hepatoma sk-Hep-1 cells at concentrations of 0.1 μM and above. No deaths were observed in mice administered 1000 mg/kg p.o. It can be extracted from plants of the genus *Panax* or produced by synthetic methods using known ginsenoside components. Another specifically claimed ginseng saponin compound is:



256492: C44-H72-O13

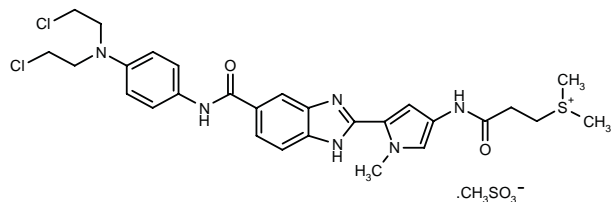
SOURCE – Cheil Foods & Chemicals.

REFERENCES

1. Lee, S.K. et al. (Cheil Je Dang Co.) *Novel ginseng saponin cpds., process for preparation thereof and anti-tumor agent comprising the same as an active component*. WO 9731933.

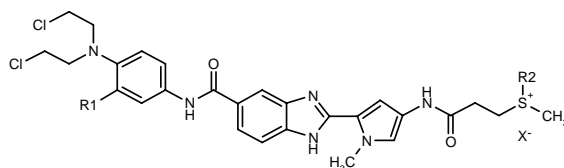
255726

S-[2-[*N*-[5-[5-[*N*-[4-[Bis(2-chloroethyl)amino]phenyl]carbamoyl]-1*H*-benzimidazol-2-yl]-1-methylpyrrol-3-yl]carbamoyl]ethyl]-*S,S*-dimethylsulfonium methanesulfonate



C29-H36-Cl2-N6-O5-S2; Mol wt: 683.67

ACTION – Antineoplastic agent with good chemical stability, giving an IC₅₀ value of 0.71 μg/ml against murine melanoma B16 cells and producing a 50% reduction in tumor weight in mice bearing colon 26 tumors at a dose of 7.19 mg/kg i.v. once a day for 15 days. Within this series of pyrrolylbenzimidazole derivatives, the following are also included:



Compound	R1	R2	X ⁻	Formula
256606	Me	Pr	mesylate	C ₃₂ H ₄₂ Cl ₂ N ₆ O ₅ S ₂
256607	H	Me	tosylate	C ₃₅ H ₄₀ Cl ₂ N ₆ O ₅ S ₂
256608	Me	Et	tosylate	C ₃₇ H ₄₄ Cl ₂ N ₆ O ₅ S ₂

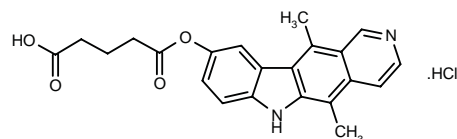
SOURCE – Mitsui Toatsu.

REFERENCES

1. Matsunaga, A. et al. (Mitsui Toatsu Chem., Inc.) *Pyrrolylbenzimidazole derivs.* JP 97208580.

256862

Glutaric acid 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazol-9-yl monoester hydrochloride



C22-H20-N2-O4.HCl; Mol wt: 412.87

ACTION – Antineoplastic agent, a potent, water-soluble prodrug of 9-hydroxyellipticine with antitumor activity against P388 leukemia (78% ILS at 70 mg/kg/day i.v. on days 1-5), colon 26 (93.8% inhibition of tumor growth at 40 mg/kg/day i.v. on days 1-7), Lewis lung carcinoma (230.4% ILS and 4/5 cures at 40 mg/kg/day i.v. on days 1-7) and B16 melanoma (68.7% ILS and 2/5 cures at 150 mg/kg/day i.v. on days 1, 5 and 9) in mice. The compound was selected as a candidate for further testing.

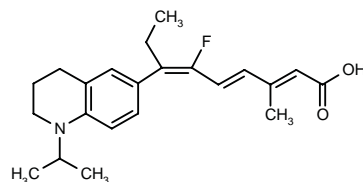
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Ellipticine derivs. with antitumor activity*. EP 608876, JP 94279441, US 5605904.
2. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Pharmaceutical compsns.* JP 96092090.
3. Harada, N. et al. *Synthesis and antitumor activity of 9-acyloxyellipticines*. Chem Pharm Bull 1997, 45(7): 1156.
4. Harada, N. et al. *Synthesis and antitumor activities of new 9-hydroxyellipticine analogues*. 16th Symp Med Chem (Nov 27-29, Toyama) 1996, Abst 2-P-16.

ER-35794**257648**

(*E,E,E*)-7-Ethyl-6-fluoro-7-(1-isopropyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-methyl-2,4,6-heptatrienoic acid



C22-H28-F-N-O2; Mol wt: 357.47

ACTION – Retinoid, the most potent retinoid X receptor (RXR)-selective agonist reported to date, as shown in transactivation assays, being more potent and selective than LGD-1069. This type of compound has been claimed in patent literature to be potentially useful in the treatment of neoplastic disorders and rheumatoid arthritis.

SOURCE – Eisai.

REFERENCES

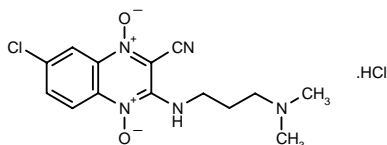
1. Hibi, S. et al. (Eisai Co., Ltd.) *Mono- or polyene-carboxylic acid derivs.* JP 96208559, WO 9613478.

2. Hibi, S. et al. *Synthesis and structure-activity relationships of novel retinoid X receptor agonists.* 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-27.

Q-85 HCl*

229116

7-Chloro-3-(3-dimethylaminopropylamino)quinoxaline-2-carbonitrile 1,4-dioxide hydrochloride



C14-H16-Cl-N5-O2.HCl; Mol wt: 358.23

Red crystalline powder, m.p. 201.1-2.2 °C.

ACTION – Hypoxia-selective antineoplastic agent, a potent, selective, water-soluble toxin that is very stable to heat and fairly stable to light. The compound demonstrated highly selective cytotoxicity to V79 cells, exhibiting a hypoxic cytotoxicity ratio (HCR; ratio of the concentration in air to the concentration in hypoxia giving 1% of control cell survival) of 250 and a potency value (P; the concentration giving 1% of control cell survival in hypoxia) of 0.4 μ M.

SOURCES – Univ. Navarra, Pamplona (ES); Zeneca.

REFERENCES

1. Monge, A. et al. *Hypoxia-selective agents derived from 2-quinoxalinecarbonitrile 1,4-di-N-oxides.* J Med Chem 1995, 38(22): 4488.

2. Zamalloa, E. et al. *Physico-chemical properties and stability of the new hypoxia-selective agent 7-chloro-3-[[N,N-dimethylamino]propyl]amino]-2-quinoxalinecarbonitrile 1,4-di-N-oxide hydrochloride.* Arzneim-Forsch-Drug Res 1997, 47(7): 873.

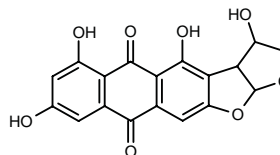
3. Zamalloa, E. et al. *Determination of a new hypoxia selective agent from 2-quinoxalinecarbonitrile 1,4-di-N-oxides in plasma by high performance liquid chromatography.* Arzneim-Forsch-Drug Res 1997, 47(9): 1044.

*Identified compound **229116** (see **229115**) Annu Drug Data Rep 1996, 18(2): 188.

UCT-1072M1

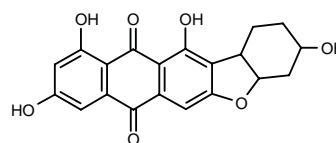
255003

3,4,6,8-Tetrahydroxy-2,3,3a,5,10,12a-hexahydroanthra[2,3-b]furo[3,2-d]furan-5,10-dione



C18-H12-O8; Mol wt: 356.29

ACTION – Antineoplastic agent produced by culturing the fungus *Aspergillus* sp. O-14-7, active *in vitro* against HeLaS3 cells (IC_{50} = 2.1 μ M) and human lung cancer Lu-65 cells (IC_{50} = 2.2 μ M). *In vivo*, it exhibited significant antitumor activity in mice bearing sarcoma 180 tumors (T/C = 0.50 at 38 mg/kg/day i.p. for 5 days). Another related compound is:



UCT-1072M2: C20-H16-O7

SOURCE – Kyowa Hakko.

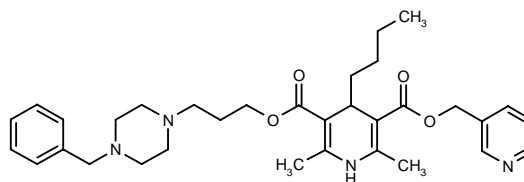
REFERENCES

1. Mizukami, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Cpds.* UCT1072. WO 9729099.

RESISTANCE MODIFIERS

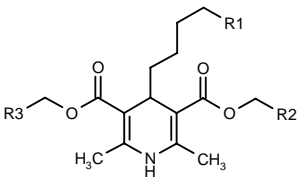
254942

4-Butyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[3-(4-benzylpiperazin-1-yl)propyl] 5-(3-pyridylmethyl) diester



C33-H44-N4-O4; Mol wt: 560.74

ACTION – Multidrug resistance-reversing agent, a dihydropyridine derivative proven to increase the sensitivity of the doxorubicin-resistant VJ300 cell line to doxorubicin at 1 μ g/ml, with superior potency to verapamil. *In vivo*, it significantly enhanced the antitumor activity of vincristine (100 μ g/kg) in vincristine-resistant P388 leukemia-bearing mice, increasing survival time from 11.2 to 17.6 days at 100 mg/kg. Compound exhibited reduced cardiovascular effects compared to verapamil and nicardipine, as demonstrated by weaker inhibition of KCl-induced rat aorta contractions (EC_{50} = 75 μ M vs. 0.59 and 0.15 μ M, respectively, for verapamil and nicardipine). LD_{50} > 700 mg/kg i.p. in mice. Other compounds from this series of dihydropyridine derivatives include the following:



Compound	R1	R2	R3	Formula
256610	H	3-Pyr	CH2N(Me)CH2Ph	C29H37N3O4
256611	Me	CH2N(Me)CH2Ph	CH2N(Me)CH2Ph	C34H47N3O4
256612	Bu	4-(PhCH2)- -1-Piz-CH2CH2	4-(PhCH2)- -1-Piz-CH2CH2	C45H67N5O4
256613	Me	4-(CO2Et)- -1-Piz-CH2CH2	4-(CO2Et)- -1-Piz-CH2CH2	C34H57N5O8
256614	Me	3-Pyr-CH=CH	4-[(Ph)2CH]- -1-Piz-CH2CH2	C42H52N4O4
256615	Me	3-Pyr-CH=CH	4-Me-5-thiazolyl-CH2	C28H35N3O4S
256616	Me	CH2N(Me)CH2Ph	4-Me-5-thiazolyl-CH2	C30H41N3O4S

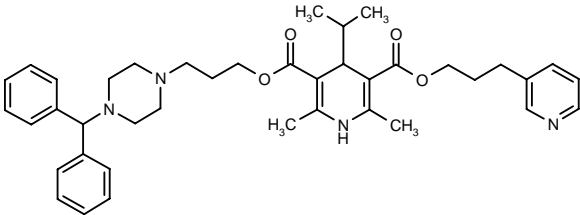
SOURCE – Nikken Chem.

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sns. containing the same. JP 97268177, WO 9728125.

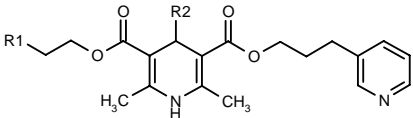
254956

4-Isopropyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[3-[4-(diphenylmethyl)piperazin-1-yl]propyl] 5-[3-(3-pyridyl)propyl] diester



C40-H50-N4-O4; Mol wt: 650.86

ACTION – Antineoplastic enhancer, a dihydropyridine derivative shown to reverse doxorubicin resistance *in vitro* in VJ-300 cells and to be devoid of significant calcium-antagonist activity (IC₅₀ = 102 μM vs. 0.26 μM for nicardipine). *In vivo*, it prolonged the life span of vincristine-resistant P388 leukemia-bearing mice when given at 100 mg/kg i.p. in combination with 100 μg/kg vincristine (T/V = 171%). A representative compound from a series of dihydropyridine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
256617	4-(PhCH2)-1-Piz-CH2	C5H11	C38H50N4O4
256619	4-[(Ph)2CH]-1-Piz-CH2	Bu	C41H52N4O4
256620	4-[(Ph)2CHCO]-1-Piz-CH2	C5H11	C43H54N4O5
256621	4-Ph-1-Piz-CH2	C5H11	C38H48N4O4
256622	4-[(Ph)2CH]-1-Piz-CH2	i-PrCH(Me)	C42H54N4O4
256623	4-[(Ph)2CH]-1-Piz-CH2	CH2CH=C(Me)2	C42H52N4O4

Compound	R1	R2	Formula
256624	4-[(Ph)2CH]-1-Piz-CH2	cyclopropyl	C40H48N4O4
256625	4-[(Ph)2CH]-1-Piz-CH2	cyclohexyl	C43H54N4O4
256626	4-[(Ph)2CH]-1-Piz-CH2	CH2CH2Ph	C45H52N4O4
256627	4-[(Ph)2CH]-1-Piz	C5H11	C41H52N4O4

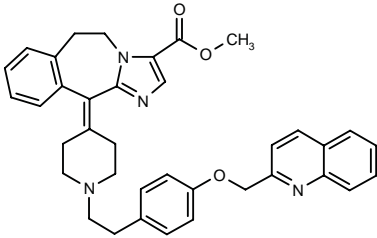
SOURCE – Nikken Chem.

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sn. comprising the same. WO 9728152.

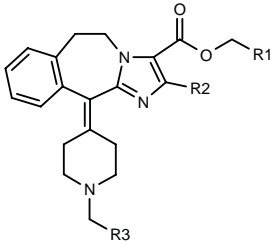
256166

11-[1-[2-[4-(2-Quinolylmethoxy)phenyl]ethyl]piperidin-4-ylidene]-6,11-dihydro-5H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid methyl ester



C37-H36-N4-O3; Mol wt: 584.72

ACTION – Multidrug resistance modulator able to reverse doxorubicin resistance in P388/ADR murine leukemia *in vivo*: median survival time was 14-23% longer than the doxorubicin monotherapy group at doses of 0.63-20 mg/kg i.p. on days 1-10 in combination with doxorubicin 1.25 mg/kg on the same schedule. Other specifically claimed fused imidazole derivatives include the following:



Compound	R1	R2	R3	Formula
257418	H	CO2Me	4-(2-quinolyl-CH2O)-PhCH2	C39H38N4O5
257419	Me	H	4-(2-quinolyl-CH2O)-PhCH2	C38H38N4O3
257420	H	H	3,5-(MeO)2-4-(2-quinolyl-CH2O)-Ph	C38H38N4O5
257421	H	H	4-(2-quinolyl-CH2O)-PhCH2CH2	C38H38N4O3
257422	H	H	4-(2-Naph-CH2O)-PhCH2	C38H37N3O3
257423	H	H	4-(PhCH2O)-PhCH2	C34H35N3O3
257424	H	H	4-(1-Naph-CH2O)-PhCH2	C38H37N3O3

SOURCE – Janssen.

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1. Janssens, F.E. et al. (Janssen Pharm. NV) Fused imidazole derivs. as multidrug
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CHEMOPROTECTIVE AGENTS

IB-367

238060

H-Arg-Gly-Gly-Leu-Cys-Tyr-Cys-Arg-Gly-Arg-Phe-Cys-Val-Cys-Val-Gly-Arg-NH₂

C78-H130-N30-O18-S4; Mol wt: 1904.32

ACTION – A synthetic protegrin antimicrobial peptide with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and *Candida albicans* (MIC = 0.13-64, 0.06-8 and 8 µg/ml, respectively). The compound was rapidly bactericidal against log- and stationary-phase cultures and did not induce resistance in methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*. It is also more potent than conventional antimicrobial agents against polymicrobial flora in human saliva. Topically administered to hamsters, it dose-dependently (0.06, 0.25 or 1.0 mg 6 times/day for 8 days) reduced the severity and duration of experimentally induced oral mucositis. Currently in phase I trials for the prevention of oral mucositis after local administration.

SOURCES – IntraBiotics; Pharmacia & Upjohn.

REFERENCES

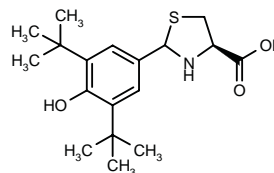
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- IB-367: IntraBiotic's first drug candidate*. Prous Science Daily Essentials July 12, 1996.
- IntraBiotics chooses drug candidate for development as treatment for oral mucositis*. IntraBiotics Pharmaceuticals, Inc. Press Release 1996, November 25.
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- IntraBiotics completes \$8.3 million second round private financing*. IntraBiotics Pharmaceuticals, Inc. Press Release 1996, June 27.
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- IntraBiotics Pharmaceuticals begins phase I safety testing of IB-367, a novel treatment for mucositis in cancer patients*. IntraBiotics Pharmaceuticals, Inc. Press Release 1997, April 8.
- IntraBiotics signs manufacturing and supply agreement for IB-367*. Prous Science Daily Essentials December 8, 1997.
- IntraBiotics/Synt:em to develop protegrin analogues*. Prous Science Daily Essentials April 2, 1997.
- Protegrin development candidate selected by IntraBiotics*. Prous Science Daily Essentials November 26, 1996.

OCULAR MEDICATIONS

ANTICATARACT AGENTS

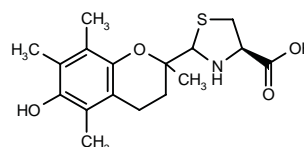
256203

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)thiazolidine-4(*R*)-carboxylic acid



C18-H27-N-O3-S; Mol wt: 337.48

ACTION – Cytoprotective agent that possesses dual activity as an antioxidant and a cysteine prodrug. It inhibited lipid peroxide formation in bovine retinal pieces, as measured by inhibition of the production of thiobarbituric acid-reacting substances (TBARS; IC₅₀ = 0.05 µM) and changes caused by oxidative damage in pigmented rabbit lens (40% inhibition of glutathione loss at 1 mM; 76% inhibition of malondialdehyde formation at 1 mM). Compound prevents or reduces tissue damage induced by oxidative stress, e.g., in disorders such as cataracts, retinopathies, glaucoma, ischemia-reperfusion damage, heart disease, cerebral ischemia, rheumatoid arthritis, cancer and atherosclerosis. Another exemplified thiazolidine-4-carboxylic acid derivative is:



257459: C17-H23-N-O4-S

SOURCE – Alcon.

REFERENCES

- Hellberg, M.R. (Alcon Labs., Inc.) *Thiazolidine-4-carboxylic acid derivs. as cytoprotective agents*. WO 9735852.

CHEMOPROTECTIVE AGENTS

IB-367

238060

H-Arg-Gly-Gly-Leu-Cys-Tyr-Cys-Arg-Gly-Arg-Phe-Cys-Val-Cys-Val-Gly-Arg-NH₂

C78-H130-N30-O18-S4; Mol wt: 1904.32

ACTION – A synthetic protegrin antimicrobial peptide with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and *Candida albicans* (MIC = 0.13-64, 0.06-8 and 8 µg/ml, respectively). The compound was rapidly bactericidal against log- and stationary-phase cultures and did not induce resistance in methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*. It is also more potent than conventional antimicrobial agents against polymicrobial flora in human saliva. Topically administered to hamsters, it dose-dependently (0.06, 0.25 or 1.0 mg 6 times/day for 8 days) reduced the severity and duration of experimentally induced oral mucositis. Currently in phase I trials for the prevention of oral mucositis after local administration.

SOURCES – IntraBiotics; Pharmacia & Upjohn.

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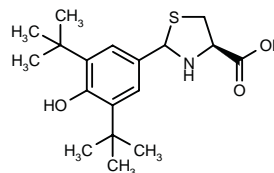
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- Protegrin development candidate selected by IntraBiotics*. Prous Science Daily Essentials November 26, 1996.

OCULAR MEDICATIONS

ANTICATARACT AGENTS

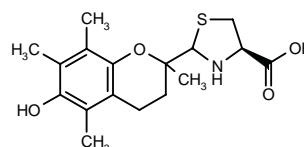
256203

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)thiazolidine-4(*R*)-carboxylic acid



C18-H27-N-O3-S; Mol wt: 337.48

ACTION – Cytoprotective agent that possesses dual activity as an antioxidant and a cysteine prodrug. It inhibited lipid peroxide formation in bovine retinal pieces, as measured by inhibition of the production of thiobarbituric acid-reacting substances (TBARS; IC₅₀ = 0.05 µM) and changes caused by oxidative damage in pigmented rabbit lens (40% inhibition of glutathione loss at 1 mM; 76% inhibition of malondialdehyde formation at 1 mM). Compound prevents or reduces tissue damage induced by oxidative stress, e.g., in disorders such as cataracts, retinopathies, glaucoma, ischemia-reperfusion damage, heart disease, cerebral ischemia, rheumatoid arthritis, cancer and atherosclerosis. Another exemplified thiazolidine-4-carboxylic acid derivative is:



257459: C17-H23-N-O4-S

SOURCE – Alcon.

REFERENCES

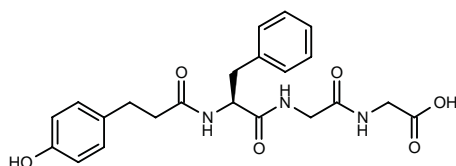
- Hellberg, M.R. (Alcon Labs., Inc.) *Thiazolidine-4-carboxylic acid derivs. as cytoprotective agents*. WO 9735852.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

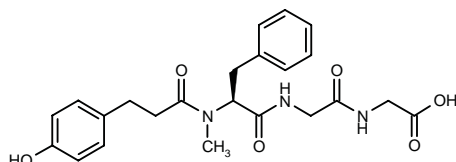
255653

3-(4-Hydroxyphenyl)propionyl-L-phenylalanyl-glycyl-glycine

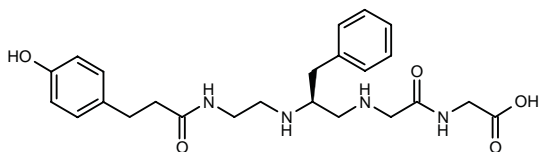


C22-H25-N3-O6; Mol wt: 427.46

ACTION – Osteogenic peptide able to enhance bone cell proliferation and bone formation. Proliferative activity was assessed *in vitro* in osteoblastic MC3T3E1 and fibroblastic NIH3T3 cells, giving relative potencies of 0.77 and 0.66 respectively (vs. 1.00 for OGP[1-14]). A particularly preferred compound within a series of specifically claimed synthetic pseudopeptide derivatives of osteogenic growth polypeptide (OGP) and OGP(10-14), wherein the following are also included:



257678: C23-H27-N3-O6



257679: C24-H32-N4-O5

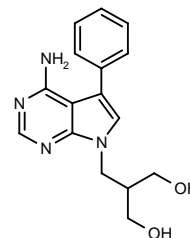
SOURCE – Yissum.

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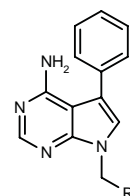
255677

2-(4-Amino-5-phenylpyrrolo[2,3-*d*]pyrimidin-7-ylmethyl)propane-1,3-diol



C16-H18-N4-O2; Mol wt: 298.34

ACTION – Agent for the treatment and prevention of osteoporosis that acts by inhibition of protein tyrosine kinase pp60^{c-src}. Also potentially useful for the treatment of tumors, tumor metastasis and inflammatory disorders. Other specifically claimed 7-alkyl-pyrrolo[2,3-*d*]pyrimidines include the following:



Compound	R1	Formula
256540	CH ₂ CH(CH ₂ OH) ₂	C ₁₇ H ₂₀ N ₄ O ₂
256541	CH(OH)CH ₂ CH ₂ OH	C ₁₆ H ₁₈ N ₄ O ₂

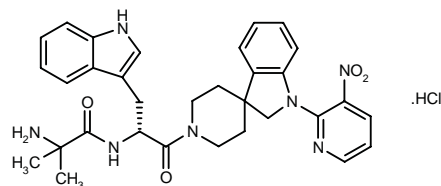
SOURCE – Novartis.

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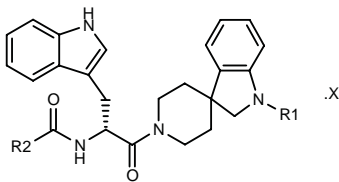
256142

1'-[N-(2-Amino-2-methylpropionyl)-D-tryptophyl]-1-(3-nitro-2-pyridyl)spiro[indoline-3,4'-piperidine] hydrochloride



C32-H35-N7-O4.HCl; Mol wt: 618.13

ACTION – Growth hormone (GH) release-promoting agent for the treatment of disorders characterized by a deficiency in GH secretion such as short stature in GH-deficient children, and for the treatment of disorders which are improved by the anabolic effects of GH, particularly osteoporosis in combination with a bisphosphonate such as alendronate. Other compounds from this series of 4-spiroindolinepiperidines include the following:



Compound	R1	R2	.X	Formula
256925	3-NH2-2-Pyr	C(Me)2NH2	2HCl	C ₃₂ H ₃₇ N ₇ O ₂ .2HCl
256926	5-NH2-1,2,4-oxadiazol-3-yl	C(Me)2NH2	CF3CO2H	C ₂₉ H ₃₄ N ₈ O ₃ .C ₂ HF ₃ O ₂
256927	5-NH2-1,2,4-triazol-3-yl	C(Me)2NH2	CF3CO2H	C ₂₉ H ₃₅ N ₉ O ₂ .C ₂ HF ₃ O ₂
256928	5-NH2-1,2,4-oxadiazol-3-yl	3(R)-Pip-NH	CF3CO2H	C ₃₁ H ₃₇ N ₉ O ₃ .C ₂ HF ₃ O ₂
256929	5-NH2-1,2,4-triazol-3-yl	3(R)-Pip-NH	CF3CO2H	C ₃₁ H ₃₈ N ₁₀ O ₂ .C ₂ HF ₃ O ₂

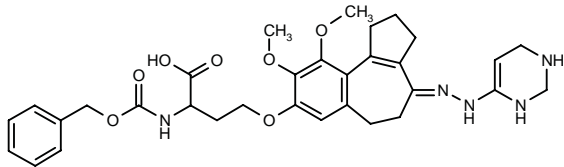
SOURCE – Merck & Co.

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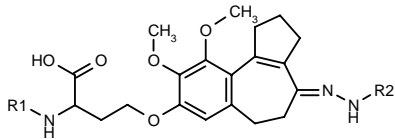
256148

2-(Benzyloxycarbonylamino)-4-[9,10-dimethoxy-4-(1,2,3,6-tetrahydropyrimidin-4-ylhydrazono)-1,2,3,4,5,6-hexahydrobenz[e]azulen-8-yloxy]butyric acid

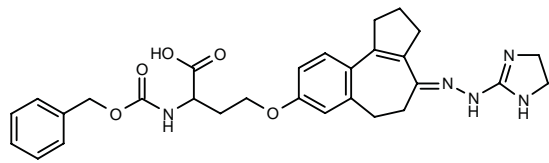


C32-H39-N5-O7; Mol wt: 605.69

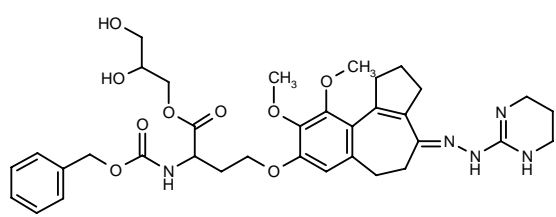
ACTION – Agent with potent and selective binding affinity for vitronectin $\alpha_v\beta_3$ receptors (IC₅₀ = 0.006 μ M) potentially useful in the treatment of osteoporosis, rheumatoid arthritis, tumors and cardiovascular disorders. Inhibition of bone resorption was evaluated in a mouse calvaria test by measuring the release of ⁴⁵Ca from the bone, giving 30% inhibition at 10 μ M. Within this series of specifically claimed tricyclic compounds, the following are also included:



Compound	R1	R2	X	Formula
256989	8-quinoliny-SO2	4,5-dihydro-2-imidazolyl		C ₃₂ H ₃₆ N ₆ O ₇ S
256990	4-(3-Pyr)-1-imidazolyl-CH2CH2CH2OCO	4,5-dihydro-2-imidazolyl	HCl	C ₃₅ H ₄₂ N ₈ O ₇ .HCl
256991	CO2CH2Ph	4,5,6,7-tetrahydro-1H-1,3-diazepin-2-yl		C ₃₃ H ₄₁ N ₅ O ₇



256987: C29-H33-N5-O5



256988: C35-H45-N5-O9

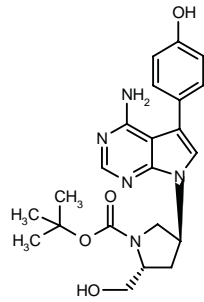
SOURCE – Hoechst Marion Roussel.

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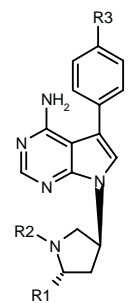
256164

(2*R*,4*S*)-4-[4-Amino-5-(4-hydroxyphenyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]-2-(hydroxymethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester



C22-H27-N5-O4; Mol wt: 425.49

ACTION – Agent for the treatment of osteoporosis, an inhibitor of protein tyrosine kinase pp60^{c-src} also claimed for use in the treatment of tumors and inflammatory disorders. A compound within a series of *N*-7-heterocyclyl-pyrrolo[2,3-*d*]pyridine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
257965	CO2Et	t-BuOCO	H	C ₂₄ H ₂₉ N ₅ O ₄
257966	CO2Et	H	H	C ₁₉ H ₂₁ N ₅ O ₂
257967	CH2OH	t-BuOCO	H	C ₂₂ H ₂₇ N ₅ O ₃
257968	CH2OH	H	H	C ₁₇ H ₁₉ N ₅ O
257969	CO2Et	t-BuOCO	OH	C ₂₄ H ₂₉ N ₅ O ₅
257970	CO2Et	H	OH	C ₁₉ H ₂₁ N ₅ O ₃
257971	CH2OH	H	OH	C ₁₇ H ₁₉ N ₅ O ₂

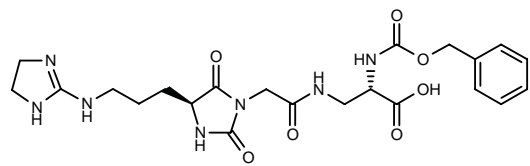
SOURCE – Novartis.

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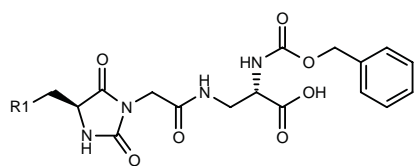
256320

2-(S)-(Benzyloxycarbonylamino)-3-[2-[4(S)-[3-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]-2,5-dioxoimidazolidin-1-yl]acetamido]propionic acid



C22-H29-N7-O7; Mol wt: 503.51

ACTION – Agent for the treatment of osteoporosis that inhibits bone resorption and acts as a vitronectin $\alpha_v\beta_3$ receptor antagonist (IC_{50} = 0.008 μ M against binding of vitronectin to human $\alpha_v\beta_3$ receptors; IC_{50} = 0.02 μ M against binding of kistrin to human $\alpha_v\beta_3$ receptors). Other representative heterocyclic compounds include the following:



Compound	R1	Formula
257400	NHCONHC(=NH)NH2	C ₁₉ H ₂₄ N ₈ O ₈
257401	2-pyrimidinyl-NHCH2CH2	C ₂₃ H ₂₇ N ₇ O ₇
257402	2-benzimidazolyl-NHCH2CH2	C ₂₆ H ₂₉ N ₇ O ₇
257403	4,5-dihydro-2-imidazolyl-NHNHCO	C ₂₁ H ₂₆ N ₈ O ₈
257404	1,4,5,6-tetrahydro-2-pyrimidinyl-NHNHCO	C ₂₂ H ₂₈ N ₈ O ₈
257405	2-benzimidazolyl-CH2	C ₂₅ H ₂₆ N ₈ O ₇
257406	CH2CONHC(=NH)NH2	C ₂₀ H ₂₅ N ₇ O ₈

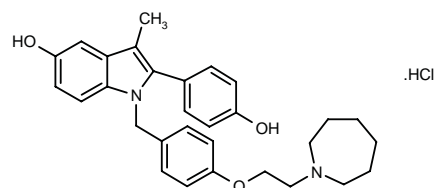
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Wehner, V. et al. (Hoechst AG) *Inhibitors of bone resorption and vitronectin receptor antagonists*. EP 796855.

256345

2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(perhydroazepin-1-yl)ethoxy]benzyl]-1H-indol-5-ol hydrochloride



C30-H34-N2-O3.HCl; Mol wt: 507.07

ACTION – Agent for the treatment of osteoporosis and cardiovascular disorders with high affinity for the estrogen receptor (IC_{50} = 50 nM). Compound exhibited antiestrogenic activity both *in vitro* in the Ishikawa alkaline phosphatase assay and *in vivo* in the immature rat uterotrophic assay, where it completely antagonized the effects of 17 β -estradiol while showing little uterine stimulation when dosed alone. Compound was estrogenic in maintaining

bone mass and lowered serum cholesterol in ovariectomized rats at 0.3 mg/kg/day p.o. x 6 weeks, being about 10-fold more potent than raloxifene, while showing little uterine stimulation. A representative compound from a series of specifically claimed indole derivatives.

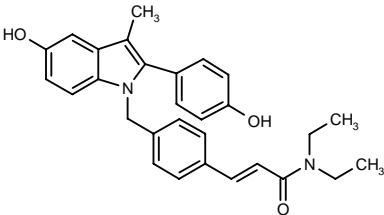
SOURCE – American Home Products.

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1. Miller, C.P. et al. (American Home Prods. Corp.) *Estrogenic agents*. EP 802183.

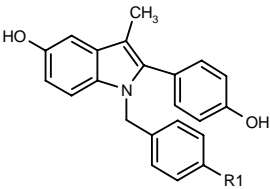
256346

N,N-Diethyl-3-[4-[5-hydroxy-2-(4-hydroxyphenyl)-3-methylindol-1-ylmethyl]phenyl]-2(E)-propenamide



C29-H30-N2-O3; Mol wt: 454.57

ACTION – Agent for the treatment of osteoporosis and cardiovascular disorders, a partial estrogen agonist with a relative binding affinity of 42 for the estrogen receptor (17 β -estradiol = 100). Compound is reported to act as an estrogen agonist to lower cholesterol and prevent bone loss, and as an antiestrogen in the uterus. A representative compound from a series of specifically claimed N-benzyl-2-phenylindoles, wherein the following are also included:



Compound	R1	Formula
257114	CH=CHCON(Bu)2	C ₃₃ H ₃₈ N ₂ O ₃
257115	CH=CHCON(Me)Bu	C ₃₀ H ₃₂ N ₂ O ₃
257116	CH=CHCONH2	C ₂₈ H ₂₂ N ₂ O ₃
257117	CH=CHCONHMe	C ₂₈ H ₂₄ N ₂ O ₃
257118	ethynylene-CH2N(Me)2	C ₂₇ H ₂₆ N ₂ O ₂
257119	1-Pip-CH2-ethynylene	C ₃₀ H ₃₀ N ₂ O ₂

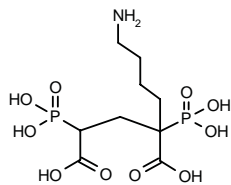
SOURCE – American Home Products.

REFERENCES

1. Miller, C.P. and Collini, M.D. (American Home Prods. Corp.) *N-Benzyl-2-phenylindoles as estrogenic agents*. EP 802184.

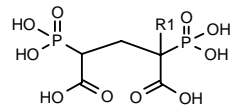
257848

2-(4-Aminobutyl)-2,4-diphosphonoglutaric acid



C9-H19-N-O10-P2; Mol wt: 363.20

ACTION – Calcium metabolism regulator with potential in the treatment of a broad range of calcium metabolism disorders, particularly diseases of the skeletal system such as osteoporosis, Paget’s disease and Bechterew’s disease. Compound was shown to produce 45% inhibition of nonstimulated bone resorption in rats at 200 mg/kg b.i.d. s.c., as assessed by [³H]-tetracycline excretion in urine. Other compounds from this series of specifically claimed 2,4-diphosphonoglutaric acid derivatives include the following:



Compound	R1	Formula
258074	Ph	C ₁₁ H ₁₄ O ₁₀ P ₂
258075	Me	C ₆ H ₁₂ O ₁₀ P ₂
258076	Bu	C ₉ H ₁₈ O ₁₀ P ₂
258077	1-pyrrolidinyl-(CH2)3	C ₁₂ H ₂₃ NO ₁₀ P ₂

SOURCE – Boehringer Mannheim.

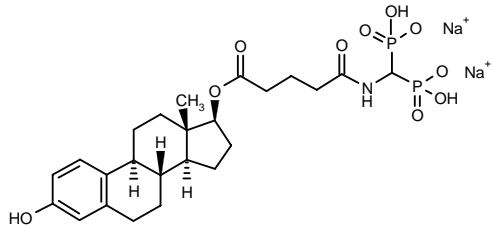
REFERENCES

1. Zimmermann, G. et al. (Boehringer Mannheim GmbH) 2,4-Diphosphonoglutaric acid derivs., processes for their production and pharmaceutical agents containing these cpds. US 5698541, WO 9526358.

E₂-BP

257457

5-[3-Hydroxyestra-1,3,5(10)trien-17β-yloxy]-5-oxopen-tanamidomethylene-1,1-diphosphonic acid disodium salt



C24-H33-N-Na2-O10-P2; Mol wt: 603.45

ACTION – Agent for the long-term estrogen replacement therapy of postmenopausal osteoporosis, a bisphosphonic produg of 17β-estradiol (E₂) that provides site-specific and sustained delivery to the bone. In ovariectomized rats, the produg was rapidly taken up in the bone after i.v. administration and exhibited a slow rate of clearance (t_{1/2} = 13.5 days), in contrast to i.v. or oral E₂ which showed low bone distribution and rapid clearance. It displayed an excellent drug targeting index and therapeutic availability, suggesting enhanced potency and an improved therapeutic index compared to E₂.

SOURCE – Fujisawa.

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1. Fujisaki, J. et al. Osteotropic drug delivery system (ODDS) based on bisphosphonic produg. V. Biological disposition and targeting characteristics of osteotropic estradiol. Biol Pharm Bull 1997, 20(11): 1183.

2. Fujisaki, J. et al. Effects of osteotropic estradiol on bone mineral density and uterine weight in ovariectomized rats. Proc Int Symp Control Release Bioact Mater 1996, 23: 613.

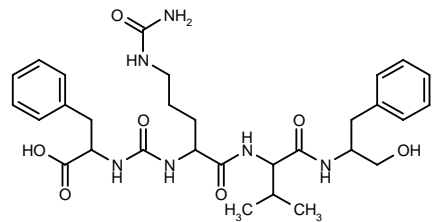
3. Tokunaga, Y. et al. Physicochemical properties and biological disposition of osteotropic estradiol. Proc Int Symp Control Release Bioact Mater 1996, 23: 615.

FA-70D

255092

2-[3-[1-[N-[1-[N-(1-Benzyl-2-hydroxyethyl)carbamoyl]-2-methylpropyl]carbamoyl]-4-ureidobutyl]ureido]-3-phenyl-propionic acid

N-[N-[1-[N-[1-[N-(1-Benzyl-2-hydroxyethyl)carbamoyl]-2-methylpropyl]carbamoyl]-4-ureidobutyl]carbamoyl]-D,L-phenylalanine



C30-H42-N6-O7; Mol wt: 598.70

ACTION – An inhibitor of cathepsin B, cathepsin L, chymotrypsin and, to a lesser degree, trypsin, produced by *Streptomyces* sp. FA-70 (FERM BP-5183), with potential in the treatment of osteoporosis.

SOURCE – Taiho.

REFERENCES

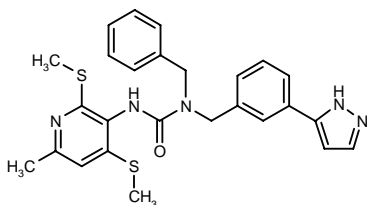
1. Kitano, S. et al. (Taiho Pharm. Co., Ltd.) Substance FA-70D, process for producing the same, and uses thereof. WO 9731122.

TREATMENT OF LIPOPROTEIN DISORDERS

FR-186054

257646

N-Benzyl-*N*'-[6-methyl-2,4-bis(methylsulfanyl)-3-pyridyl]-*N*-[3-(2*H*-pyrazol-3-yl)benzyl]urea



C26-H27-N5-O-S2; Mol wt: 489.65

ACTION – Hypolipidemic and antiatherosclerotic agent, an orally active ACAT inhibitor with potent *in vitro* activity (IC_{50} = 99 nM) and excellent serum cholesterol-lowering efficacy in cholesterol-fed rats (ED_{50} = 0.046 mg/kg p.o.).

SOURCE – Fujisawa.

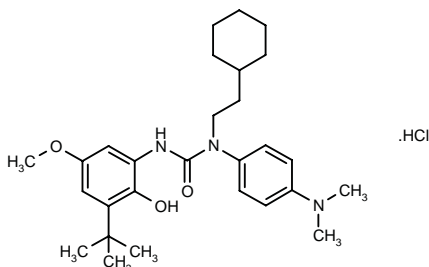
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1. Terasawa, T. et al. (Fujisawa Pharm. Co., Ltd.) *Urea derivs. and their use as ACAT-inhibitors*. WO 9610559.
2. Tanaka, A. et al. *Discovery of FR186054, a novel, potent, orally active inhibitor of acyl-CoA:cholesterol O-acyltransferase (ACAT)*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-19.

T-2591

256072

N-[3-(*tert*-Butyl)-2-hydroxy-5-methoxyphenyl]-*N*'-(2-cyclohexylethyl)-*N*'-[4-(dimethylamino)phenyl]urea hydrochloride



C28-H41-N3-O3.HCl; Mol wt: 504.11

ACTION – Potential antiatherosclerotic agent, a ureidophenol derivative proven to inhibit LDL oxidation induced by copper (complete inhibition at 10 μ M) or endothelial cells (0.1 μ M or more) and ACAT from rabbit intestine, liver and aorta (IC_{50} = 0.26, 4.6 and 4.1 μ M, respectively) and mouse macrophage J774 A.1 cells (IC_{50} = 0.067 μ M). The compound also inhibited foam cell formation in mouse peritoneal macrophages and J774 A.1 cells (IC_{50} = 0.06 and 0.44 μ M, respectively).

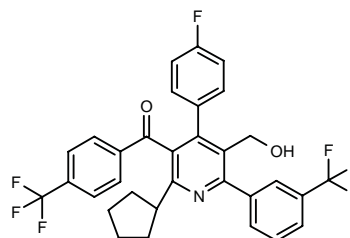
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Suzuki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Phenol-derivs. having pharmaceutical activity and process for preparing the same*. EP 790240.
2. Yasuhara, M. et al. *Inhibitory effect of a new ureidophenol derivative T-2591 on LDL oxidation and ACAT activity*. Biol Pharm Bull 1997, 20(10): 1056.

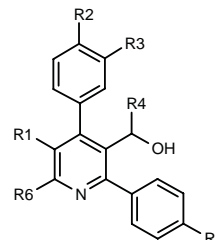
256316

1-[2-Cyclopentyl-4-(4-fluorophenyl)-5-(hydroxymethyl)-6-[3-(trifluoromethyl)phenyl]pyridin-3-yl]-1-[4-(trifluoromethyl)phenyl]methanone



C32-H24-F7-N-O2; Mol wt: 587.54

ACTION – Hypolipidemic and antiatherosclerotic agent that acts by inhibiting cholesteryl ester transfer protein (CETP; IC_{50} = 70 nM). Other representative compounds within this series of 2-aryl-substituted pyridines include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
257407	4-CF3-PhCHF	F	H	Me	F	i-Pr	C ₃₀ H ₂₈ F ₆ NO
257408	4-CF3-PhCO	F	H	Me	F	cyclopentyl	C ₃₂ H ₂₆ F ₅ NO ₂
257409	4-CF3-PhCHF	F	H	H	F	i-Pr	C ₂₉ H ₂₃ F ₆ NO
257410	4-CF3-PhCHF	F	H	H	Cl	cyclopentyl	C ₃₁ H ₂₅ ClF ₅ NO
257411	4-CF3-PhCHF	F	H	H	F	cyclopentyl	C ₃₁ H ₂₅ F ₆ NO
257412	2,4-(CF3)2-PhCHF	F	H	H	F	cyclopentyl	C ₃₂ H ₂₄ F ₉ NO
257413	4-CF3-PhCHF	F	H	H	F	cyclohexyl	C ₃₂ H ₂₇ F ₆ NO
257414	4-CF3-PhCHF	F	H	H	F	cycloheptyl	C ₃₃ H ₂₉ F ₆ NO
257415	4-CF3-PhCHF	H	Cl	H	F	i-Pr	C ₂₉ H ₂₄ ClF ₄ NO
257416	2-Naph-CHF	F	H	H	F	cyclopentyl	C ₃₄ H ₂₈ F ₃ NO
257417	3-CF3-PhCH=CH	F	H	H	F	i-Pr	C ₃₀ H ₂₄ F ₅ NO

SOURCE – Bayer.

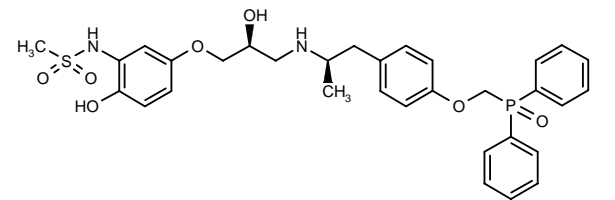
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1. Schmidt, G. et al. (Bayer AG) *2-Aryl subst. pyridines*. EP 796846.

ANTIOBESITY DRUGS

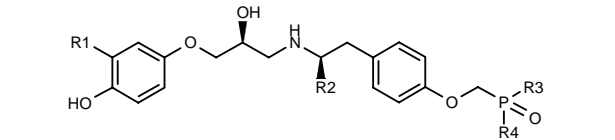
256170

N-[5-[3-[2-[4-(Diphenylphosphorylmethoxy)phenyl]-1(*R*)-methylethylamino]-2(*S*)-hydroxypropoxy]-2-hydroxy-phenyl]methanesulfonamide



C32-H37-N2-O7-P-S; Mol wt: 624.69

ACTION – Antiobesity and hypoglycemic agent, a β_3 -adrenoceptor agonist with selectivity for β_3 -adrenoceptors. Agonist activity at β_3 -adrenoceptors was demonstrated by its ability to stimulate adenylyl cyclase activity in CHO cells expressing the human β_3 -adrenoceptor (EC_{50} = 0.01 μ M), and β_1 - and β_2 -adrenoceptor agonism was assessed in a binding assay using CHO cells transfected with the human receptors and [¹²⁵I]-iodocyanopindolol as the radioligand (K_i = 0.13 and 0.12 μ M, respectively). Compound is reported to show reduced cardiac and tremorigenic side effects and to exhibit good bioavailability. Within this series of specifically claimed phosphine oxide propanolamine derivatives, the following are also included:



Compound	R1	R2	R3=R4	Formula
256955	H	H	Ph	C ₃₀ H ₃₂ NO ₅ P
256956	NHSO ₂ Me	Me	(CH ₂) ₃ Ph	C ₃₈ H ₄₉ N ₂ O ₇ PS

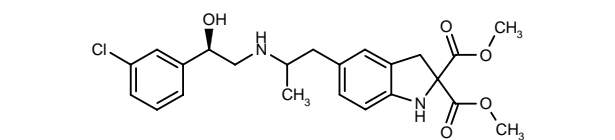
SOURCE – SmithKline Beecham.

REFERENCES

1. Morgan, H.K.A. et al. (SmithKline Beecham plc) *Phosphorus containing aryloxy and arylthiopropanol amine derivs. useful as β adrenoreceptor agonists.* WO 9734905.

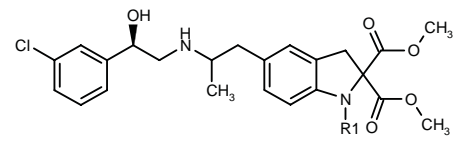
256339

5-[2-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethylamino]propyl]-indoline-2,2-dicarboxylic acid dimethyl ester

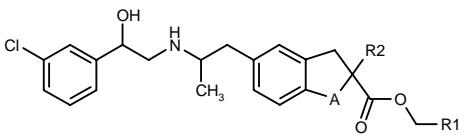


C23-H27-Cl-N2-O5; Mol wt: 446.93

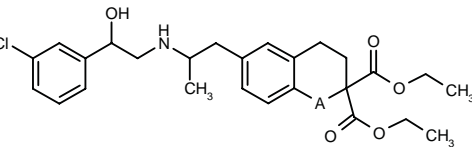
ACTION – Antiobesity and hypoglycemic agent, a β_3 -adrenoceptor agonist with marked selectivity over β_2 - and β_1 -adrenoceptors. Other exemplified heterocyclic compounds include the following:



Compound	R1	Formula
257038	SO ₂ Ph	C ₂₉ H ₃₁ ClN ₂ O ₇ S
257039	COPh	C ₃₀ H ₃₁ ClN ₂ O ₆
257040	CH ₂ Ph	C ₃₀ H ₃₃ ClN ₂ O ₅
257041	Ac	C ₂₅ H ₂₉ ClN ₂ O ₆
257042	COCH ₂ Ph	C ₃₁ H ₃₃ ClN ₂ O ₆
257043	Et	C ₂₅ H ₃₁ ClN ₂ O ₅
257044	Me	C ₂₄ H ₂₉ ClN ₂ O ₅



Compound	R1	R2	A	Formula
257045	H	H	N(COPh)	C ₂₈ H ₂₉ ClN ₂ O ₄
257047	Me	CO ₂ Et	O	C ₂₅ H ₃₀ ClNO ₆
257049	H	H	N(CH ₂ Ph)	C ₂₈ H ₃₁ ClN ₂ O ₃



Compound	A	Formula
257046	O	C ₂₆ H ₃₂ ClNO ₆
257048	N(CH ₂ Ph)	C ₃₃ H ₃₉ ClN ₂ O ₅

SOURCE – Pfizer.

REFERENCES

1. Dow, R.L. and Wright, S.W. (Pfizer, Inc.) *Heterocyclic β -3 adrenergic agonists.* EP 801060.

FIBULIN TYPE 1

257226

ACTION – Agent for the treatment of obesity, hyperlipidemia and type II diabetes, a peptide found in plasma and known to bind to various extracellular matrix proteins such as fibronectin, laminin and nidogen, now reported to enhance the effectiveness of exogenously administered or endogenous OB protein. Compound is believed to act by binding to OB protein, which results in an increase in the stability of OB protein in the blood. Also claimed is the use of a complex with OB protein.

SOURCE – Amgen.

REFERENCES

1. Bennett, L.G. (Amgen, Inc.) *Fibulin pharmaceutical compsns. and related methods.* WO 9738014.

HUMAN CACHEXIA-ASSOCIATED PROTEIN

257227

HCAP

ACTION – Agent for the treatment of severe to moderate obesity, a human cachexia-associated protein (HCAP) whose nucleic acid sequence was identified among the polynucleotides from a breast tumor library. Also claimed are antisense molecules, antibodies, antagonists and inhibitors of HCAP for the treatment of tumor-induced cachexia.

SOURCE – Incyte.

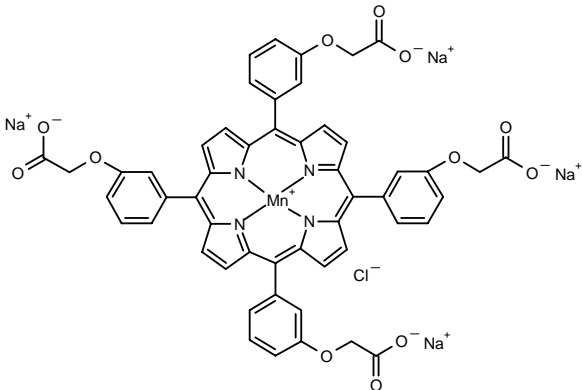
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DIAGNOSTIC AGENTS

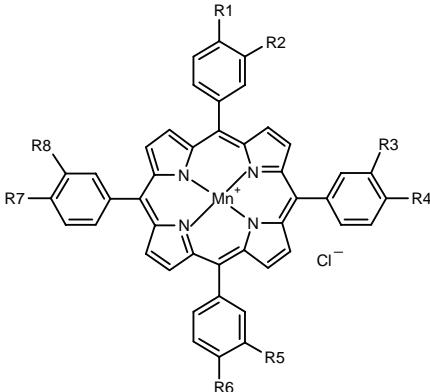
255191

[5,10,15,20-Tetrakis[3-(carboxymethoxy)phenyl]-21,23-porphyrinate]manganese(III) chloride tetrasodium salt



C52-H32-Cl-Mn-N4-Na4-O12; Mol wt: 1087.19

ACTION – Meso-tetraphenylporphyrin manganese(III) complex for use as a nuclear magnetic resonance (NMR) diagnostic agent, particularly for the imaging of tumors. Other related complexes include the following:



Compound	R1=R4=R6=R7	R2=R3=R5=R8	Formula
255373	OCH2CO2Na	H	C ₅₂ H ₃₂ ClMnN ₄ Na ₄ O ₁₂
255374	OCH2CO2H	OCH2CO2H	C ₆₀ H ₄₄ ClMnN ₄ O ₂₄

Compound	R1=R4=R6=R7	R2=R3=R5=R8	Formula
255375	H	H	C ₆₀ H ₄₄ ClMnN ₄ Na ₄ O ₁₂
255376	H	CH2CO2H	C ₅₂ H ₃₆ ClMnN ₄ O ₈
255377	H	N(CH2CO2H)2	C ₆₀ H ₄₈ ClMnN ₈ O ₁₆

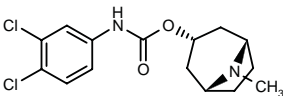
SOURCE – Inst. Diagnostikforschung, Berlin (DE).

REFERENCES

1. Maier, F.K. et al. (Inst. Diagnostikforschung GmbH) *Meso-tetraphenylporphyrin complex cpds., process for their production and pharmaceutical agents containing the lat-ter*. US 5674467, WO 9419352.

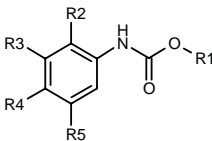
256161

endo-N-(3,4-Dichlorophenyl)carbamic acid 8-methyl-8-azabicyclo[3.2.1]octan-3-yl ester



C15-H18-Cl2-N2-O2; Mol wt: 329.23

ACTION – Compound with high affinity and selectivity for σ_2 -receptors (K_i = 36.9 nM vs. > 1000 nM for σ_1 -recep-tors). Labeled compound is useful for detecting cancer cells or assessing the proliferative status of cancer cells expressing σ_2 -receptors, such as breast cancer cells. Other specifically claimed compounds include the follow-ing:



Compound	R1	R2	R3	R4	R5	Formula
257425	endo-8-Me-8-aza-bicyclo[3.2.1]oct-3-yl	OMe	H	H	Cl	C ₁₆ H ₂₁ ClN ₂ O ₃
257426	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	H	Cl	Cl	H	C ₂₂ H ₂₄ Cl ₂ N ₂ O ₂
257427	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	H	OMe	C ₂₄ H ₃₀ N ₂ O ₄
257428	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	OMe	Cl	C ₂₄ H ₂₉ ClN ₂ O ₄
257429	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	H	Cl	C ₂₃ H ₂₇ ClN ₂ O ₃
257430	endo-9-Me-9-aza-bicyclo[3.3.1]non-3-yl	H	Cl	Cl	H	C ₁₆ H ₂₆ Cl ₂ N ₂ O ₂
257431	endo-8-(PhCH2)-8-aza-bicyclo[3.2.1]oct-3-yl	OMe	H	H	OMe	C ₂₃ H ₂₈ N ₂ O ₄
257432	endo-8-(PhCH2)-8-aza-bicyclo[3.2.1]oct-3-yl	H	Cl	Cl	H	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₂
257433	endo-9-Me-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	H	OMe	C ₁₈ H ₂₆ N ₂ O ₄

SOURCE – Wake Forest Univ., Winston-Salem, NC (US).

REFERENCES

1. Mach, R.H. et al. (Wake Forest Univ.) *σ -2 Receptors as biomarkers of tumor cell pro-liferation*. WO 9734892.

HUMAN CACHEXIA-ASSOCIATED PROTEIN

257227

HCAP

ACTION – Agent for the treatment of severe to moderate obesity, a human cachexia-associated protein (HCAP) whose nucleic acid sequence was identified among the polynucleotides from a breast tumor library. Also claimed are antisense molecules, antibodies, antagonists and inhibitors of HCAP for the treatment of tumor-induced cachexia.

SOURCE – Incyte.

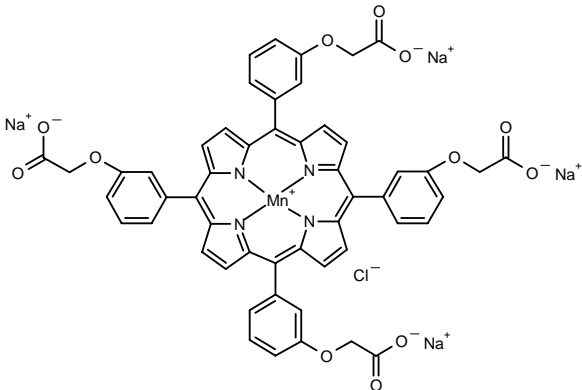
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DIAGNOSTIC AGENTS

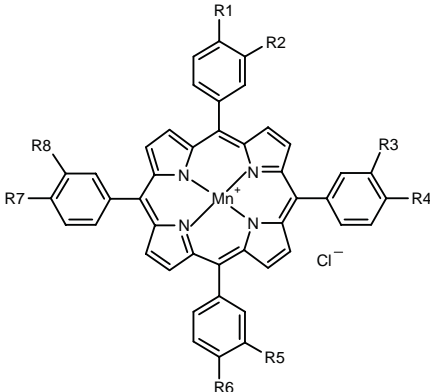
255191

[5,10,15,20-Tetrakis[3-(carboxymethoxy)phenyl]-21,23-porphyrinate]manganese(III) chloride tetrasodium salt



C52-H32-Cl-Mn-N4-Na4-O12; Mol wt: 1087.19

ACTION – Meso-tetraphenylporphyrin manganese(III) complex for use as a nuclear magnetic resonance (NMR) diagnostic agent, particularly for the imaging of tumors. Other related complexes include the following:



Compound	R1=R4=R6=R7	R2=R3=R5=R8	Formula
255373	OCH2CO2Na	H	C ₅₂ H ₃₂ ClMnN ₄ Na ₄ O ₁₂
255374	OCH2CO2H	OCH2CO2H	C ₆₀ H ₄₄ ClMnN ₄ O ₂₄

Compound	R1=R4=R6=R7	R2=R3=R5=R8	Formula
255375	H	H	C ₆₀ H ₄₄ ClMnN ₄ Na ₄ O ₁₂
255376	H	CH2CO2H	C ₅₂ H ₃₆ ClMnN ₄ O ₈
255377	H	N(CH2CO2H)2	C ₆₀ H ₄₈ ClMnN ₈ O ₁₆

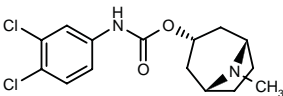
SOURCE – Inst. Diagnostikforschung, Berlin (DE).

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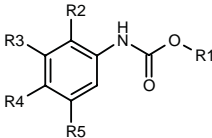
256161

endo-N-(3,4-Dichlorophenyl)carbamic acid 8-methyl-8-azabicyclo[3.2.1]octan-3-yl ester



C15-H18-Cl2-N2-O2; Mol wt: 329.23

ACTION – Compound with high affinity and selectivity for σ_2 -receptors (K_i = 36.9 nM vs. > 1000 nM for σ_1 -recep-tors). Labeled compound is useful for detecting cancer cells or assessing the proliferative status of cancer cells expressing σ_2 -receptors, such as breast cancer cells. Other specifically claimed compounds include the follow-ing:



Compound	R1	R2	R3	R4	R5	Formula
257425	endo-8-Me-8-aza-bicyclo[3.2.1]oct-3-yl	OMe	H	H	Cl	C ₁₆ H ₂₁ ClN ₂ O ₃
257426	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	H	Cl	Cl	H	C ₂₂ H ₂₄ Cl ₂ N ₂ O ₂
257427	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	H	OMe	C ₂₄ H ₃₀ N ₂ O ₄
257428	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	OMe	Cl	C ₂₄ H ₂₉ ClN ₂ O ₄
257429	endo-9-(PhCH2)-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	H	Cl	C ₂₃ H ₂₇ ClN ₂ O ₃
257430	endo-9-Me-9-aza-bicyclo[3.3.1]non-3-yl	H	Cl	Cl	H	C ₁₆ H ₂₆ Cl ₂ N ₂ O ₂
257431	endo-8-(PhCH2)-8-aza-bicyclo[3.2.1]oct-3-yl	OMe	H	H	OMe	C ₂₃ H ₂₈ N ₂ O ₄
257432	endo-8-(PhCH2)-8-aza-bicyclo[3.2.1]oct-3-yl	H	Cl	Cl	H	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₂
257433	endo-9-Me-9-aza-bicyclo[3.3.1]non-3-yl	OMe	H	H	OMe	C ₁₈ H ₂₆ N ₂ O ₄

SOURCE – Wake Forest Univ., Winston-Salem, NC (US).

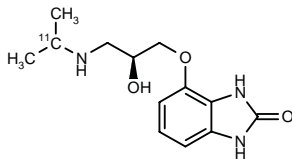
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(S)-[¹¹C]-CGP-12388

257094

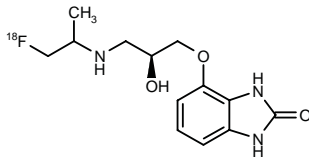
4-[2(S)-Hydroxy-3-([2-¹¹C]-isopropylamino)propoxy]benzimidazolin-2-one



C12-¹¹C-H19-N3-O3; Mol wt: 264.30

Unlabeled hydrochloride salt, m.p. 231-2 °C.

ACTION – β-Adrenoceptor ligand for clinical positron emission tomography (PET) in lung and heart. (S)-[¹¹C]-CGP-12388 is easily synthesized and shows good lipophilicity, which would facilitate penetration through the blood–brain barrier. *In vivo* biodistribution studies in rats with (S)-[¹¹C]-CGP-12388 and (S)-[¹⁸F]-CGP-12388 showed specific binding to β-adrenoceptors in lung and heart tissues, and lungs were clearly visualized in PET studies. (S)-[¹¹C]-CGP-12388 showed a superior biodistribution profile compared to the [¹⁸F]-labeled compound.



(S)-[¹⁸F]-Fluoro-CGP-12388 [257095]: C13-H18-¹⁸F-N3-O3

SOURCE – Novartis.

REFERENCES

1. Elsinga, P.H. et al. *Synthesis and evaluation of (S)-4-(3-(2'-[¹¹C]isopropylamino)-2-hydroxypropoxy)-2H-benzimidazol-2-one ((S)-[¹¹C]CGP 12388) and (S)-4-(3-((1'-[¹⁸F]fluoroisopropyl)amino)-2-hydroxypropoxy)-2H-benzimidazol-2-one ((S)-[¹⁸F]fluoro-CGP 12388) for visualization of beta-adrenoceptors with positron emission tomography.* J Med Chem 1997, 40(23): 3829.

2. Elsinga, P.H. et al. *(C-11)- and (F-18)-Labelled (S)-CGP 12388: New tracers for visualization of beta-adrenoceptors with positron emission tomography.* J Nucl Med 1997, 38(5, Suppl.): Abst 281.

MANGAFODIPIR TRISODIUM

Rec INNM; BAN

172203

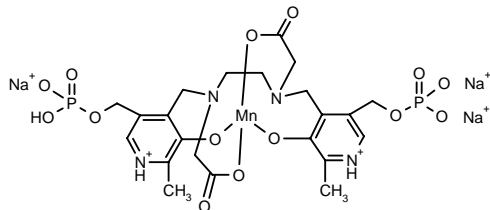
Trisodium trihydrogen (OC-6-13)-[[N,N'-1,2-ethanediyl-bis[N-[[3-hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycinato](8-)]manganate(6-)

Manganese dipyridoxal diphosphate trisodium salt

MnDPDP⁺

S-095

Win-59010-2



C22-H27-Mn-N4-Na3-O14-P2; Mol wt: 757.33

ACTION – Paramagnetic MRI contrast medium.

INDICATION – Diagnostic MRI for the detection of lesions of the liver suspected to be due to metastatic disease or hepatocellular carcinomas.

PRESENTATION – Vials containing solution for i.v. infusion (50 ml), 0.01 mmol/ml.

PROPRIETARY NAME – *Teslascan* (AT, DE, GB, SE).

SOURCE – Nycomed Amersham.

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5. Grant, D. et al. *Tissue distribution and general safety of MnDPDP in male beagle dogs, with or without total common bile duct obstruction* Acta Radiol 1997, 38(4, Part 2): 732.

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27. Torres, C.G. et al. *MnDPDP for MR imaging of the liver - Results from the European phase III studies.* Acta Radiol 1997, 38(4, Part 2): 631.

28. Towart, R. et al. *Cardiovascular safety of intravenously administered MnDPDP as compared to $MnCl_2$ in the conscious beagle dog.* Brit J Pharmacol 1997, 120(Suppl.): Abst 158P.

29. Wang, C. et al. *Diagnostic efficacy of MnDPDP in MR imaging of the liver - A phase III multicentre study.* Acta Radiol 1997, 38(4, Part 2): 643.

30. Wang, C. et al. *MR imaging properties and pharmacokinetics of MnDPDP in healthy volunteers.* Acta Radiol 1997, 38(4, Part 2): 665.

31. *FDA clears Teslascan for detection of liver diseases.* Prous Science Daily Essentials December 10, 1997.

32. *First approval for new MRI contrast agent from Nycomed.* Prous Science Daily Essentials June 6, 1997.

33. *New MRI contrast agent available in Europe.* Prous Science Daily Essentials October 28, 1997.

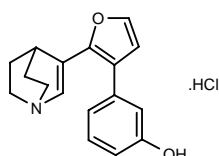
MONOGRAPH – Graul, A. et al. *Mangafodipir trisodium.* Drugs Fut 1997, 22(9): 974.

*Annu Drug Data Rep 1991, 13(9): 818.

PHARMACOLOGICAL TOOLS

257086

3-[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)furan-3-yl]phenol hydrochloride



C17-H17-N-O2.HCl; Mol wt: 303.79

M.p. 220-2 °C.

ACTION – Antimuscarinic agent from a series of 3-(2-furanyl)quinuclidin-2-ene derivatives with affinity for muscarinic receptors in guinea pig cerebral cortex, heart and parotid gland ($K_i = 0.27 \pm 0.06$, 0.72 ± 0.20 and 0.61 ± 0.01 nM, respectively, using (–)-[³H]-QNB as the radioligand). SAR of this type of compound demonstrate that the affinity of a previously described furan derivative (EN:204690⁺) can be enhanced more than 1000-fold by appropriate substitution in the furan ring.

SOURCE – Pharmacia & Upjohn.

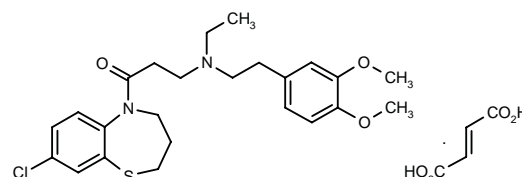
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*Annu Drug Data Rep 1994, 16(4): 323.

257452

8-Chloro-5-[3-[*N*-ethyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-amino]propionyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine fumarate



C24-H31-Cl-N2-O3-S.C4-H4-O4; Mol wt: 579.11

M.p. 123-4 °C.

ACTION – Compound derived from the intracellular Ca^{2+} antagonist KT-362 that exerts potent vascular smooth muscle contractile activity, as demonstrated in rabbit iliac artery ($ED_{50} = 34.7$ nM). Its effect appears to be mediated by a Ca^{2+} -agonist action, although activation of histamine H_1 receptors may also be involved.

SOURCE – Kotobuki.

REFERENCES

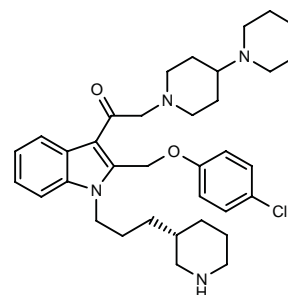
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LY-357897

257093

2-(4-Chlorophenoxyethyl)-3-[2-[4-(1-piperidyl)piperidin-1-yl]acetyl]-1-[3-[piperidin-3(*S*)-yl]propyl]indole



C35-H47-Cl-N4-O2; Mol wt: 591.23

23. Toft, K.G. et al. *Metabolism of mangafodipir trisodium (MnDPDP), a new contrast medium for magnetic resonance imaging, in beagle dogs.* Eur J Drug Metab Pharmacokinet 1997, 22(1): 65.

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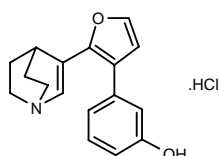
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PHARMACOLOGICAL TOOLS

257086

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M.p. 220-2 °C.

ACTION – Antimuscarinic agent from a series of 3-(2-furanyl)quinuclidin-2-ene derivatives with affinity for muscarinic receptors in guinea pig cerebral cortex, heart and parotid gland ($K_i = 0.27 \pm 0.06$, 0.72 ± 0.20 and 0.61 ± 0.01 nM, respectively, using (–)-[3H]-QNB as the radioligand). SAR of this type of compound demonstrate that the affinity of a previously described furan derivative (EN:204690⁺) can be enhanced more than 1000-fold by appropriate substitution in the furan ring.

SOURCE – Pharmacia & Upjohn.

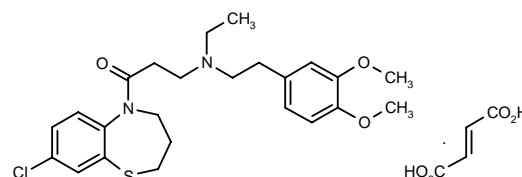
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*Annu Drug Data Rep 1994, 16(4): 323.

257452

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C24-H31-Cl-N2-O3-S.C4-H4-O4; Mol wt: 579.11

M.p. 123-4 °C.

ACTION – Compound derived from the intracellular Ca^{2+} antagonist KT-362 that exerts potent vascular smooth muscle contractile activity, as demonstrated in rabbit iliac artery ($ED_{50} = 34.7$ nM). Its effect appears to be mediated by a Ca^{2+} -agonist action, although activation of histamine H_1 receptors may also be involved.

SOURCE – Kotobuki.

REFERENCES

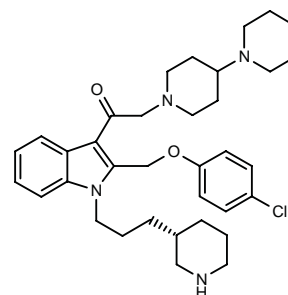
1. Tomiyama, T. et al. (Kotobuki Seiyaku Co., Ltd.) *1,5-Benzothiazepine derivs. as cardiotonics and their preparation.* JP 93065278.

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LY-357897

257093

2-(4-Chlorophenoxymethyl)-3-[2-[4-(1-piperidyl)piperidin-1-yl]acetyl]-1-[3-[piperidin-3(*S*)-yl]propyl]indole



C35-H47-Cl-N4-O2; Mol wt: 591.23

ACTION – Potent and selective neuropeptide Y (NPY) Y_1 receptor antagonist, as shown in binding studies using human cloned Y_1 receptors ($K_i = 0.75 \pm 0.02$ nM) and Y_2 , Y_3 and Y_4 receptors ($K_i > 10$ μ M). Functional antagonist activity at the Y_1 receptor was demonstrated by reversal of NPY-induced inhibition of forskolin-stimulated cAMP and inhibition of NPY-induced intracellular Ca^{2+} mobilization in SK-N-MC cells. Likewise, it was able to inhibit NPY-induced food consumption in mice ($ED_{50} = 17$ nmol i.c.v.), without affecting neuromuscular function. However, serum levels of LY-357897 after p.o. or s.c. administration were insufficient for evaluating the compound systemically in this model. Potentially useful as a tool for elucidating the role of the Y_1 receptor subtype.

SOURCE – Lilly.

REFERENCES

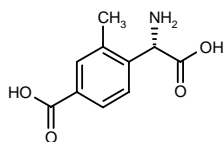
1. Hipskind, P.A. et al. *Potent and selective 1,2,3-trisubstituted indole NPY Y-1 antagonists*. J Med Chem 1997, 40(23): 3712.

LY-367385

256894

(+)-(S)-4-(1-Amino-1-carboxymethyl)-3-methylbenzoic acid

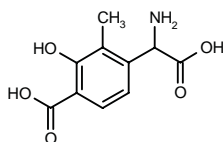
(+)-2MCPG



C10-H11-N-O4; Mol wt: 209.20

$[\alpha]_D^{25} + 147^\circ$ (c 0.26, 5M HCl).

ACTION – Potent metabotropic glutamate receptor (mGluR1 α) antagonist with greater potency than (S)-4-carboxyphenylglycine for inhibiting quisqualate-induced phosphoinositide hydrolysis in AV-12 cells ($IC_{50} = 8.8 \pm 3.9$ μ M vs. 58 ± 14 μ M) and good selectivity over mGluR5a and group 2 mGluRs ($IC_{50} > 100$ μ M). Potentially useful as a pharmacological tool for elucidating the physiological role of this receptor. Another compound from this series of 4-carboxyphenylglycine derivatives is:



256895: C10-H11-N-O5

SOURCE – Lilly.

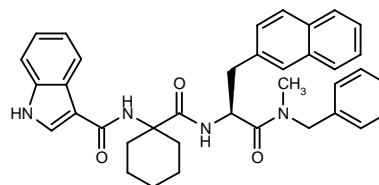
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MEN-10930

256880

N-[1-(1H-Indol-3-ylcarboxamido)cyclohexan-1-ylcarbonyl]-3-(2-naphthyl)-L-alanine N-benzyl-N-methylamide



C37-H38-N4-O3; Mol wt: 586.73

ACTION – Potent, competitive and specific human tachykinin NK $_1$ receptor antagonist, as demonstrated in binding studies using [3 H]-substance P as the ligand and NK $_1$ receptors expressed in human lymphoblastoma IM9 cells ($K_i = 1.0 \pm 0.17$ nM) and human astrocytoma U373MG cells ($K_i = 2.8 \pm 0.5$ nM), as well as guinea pig lung membranes ($K_i = 5.9 \pm 0.8$ nM); however, it showed no affinity for NK $_1$ receptors in rat urinary bladder membranes ($K_i > 10,000$ nM), at least 3 orders of magnitude less affinity for NK $_2$ ($K_i = 1.5 \pm 0.5$ μ M) and NK $_3$ receptors ($K_i > 10$ μ M), and negligible affinity for the L-type voltage-sensitive calcium channel ($K_i = 1.6 \pm 0.6$ μ M). Functional studies demonstrated concentration-dependent inhibition of substance P methyl ester-induced contractions in guinea pig ileum ($pA_2 = 8.7 \pm 0.08$). MEN-10930 may thus represent a useful pharmacological tool for investigating NK $_1$ receptor heterogeneity and for characterizing mutated forms of this receptor.

SOURCES – Malesci; Menarini.

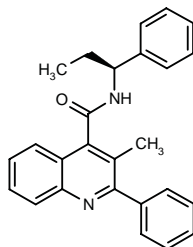
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SB-222200***231645**

(–)-3-Methyl-2-phenyl-*N*-[1(*S*)-phenylpropyl]quinoline-4-carboxamide

(–)-(*S*)-*N*-(α -Ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboxamide



C26-H24-N2-O; Mol wt: 380.49

ACTION – Potent, selective, competitive and orally active, nonpeptide neurokinin NK₃ receptor antagonist, as demonstrated in binding studies ($K_i = 4.2 \pm 0.6$ nM for displacement of [¹²⁵I]-[MePhe⁷]-NKB binding in human NK₃ receptor-expressing CHO cell membranes; $K_i = 277 \pm 57$ and $> 100,000$ nM, respectively, in CHO cells expressing human NK₂ and NK₃ receptors), and against senktide-induced contractions in rabbit isolated iris sphincter muscle ($K_b = 7.7$ nM). *In vivo*, it antagonized senktide-induced behavioral responses in mice ($ED_{50} = 5.6$ mg/kg p.o.) and senktide-induced bilateral miosis in rabbits (1 and 2 mg/kg i.v.). The compound also appears to be a potent and selective antagonist at the putative “NK₄” receptor. In rats dosed orally (8 mg/kg), it gave sustained plasma levels and readily crossed the blood–brain barrier. Potentially useful as a pharmacological tool for elucidating the functional and pathophysiological role of NK₃ receptors.

SOURCE – SmithKline Beecham.

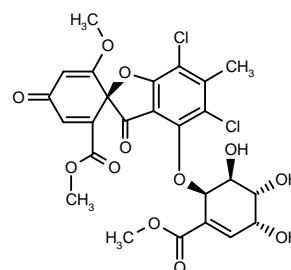
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*Identified compound **231645** Annu Drug Data Rep 1996, 18(3): 232.

SCH-202596**256087**

(2*S*)-5,7-Dichloro-6'-methoxy-6-methyl-3,4'-dioxo-4-[4(*R*),5(*R*),6(*S*)-trihydroxy-2-(methoxycarbonyl)-2-cyclohexen-1(*R*)-yloxy]spiro[benzofuran-2(3*H*),1'-2',5'-cyclohexadiene]-2'-carboxylic acid methyl ester



C25-H22-Cl2-O12; Mol wt: 585.35

Pale yellow solid, m.p. 136-8 °C, $[\alpha]_D^{22} +235.4^\circ$ (c 0.1, MeOH).

ACTION – Fungal metabolite isolated from the fermentation broth of *Aspergillus* sp. with inhibitory activity in the galanin receptor (GALR1) assay ($IC_{50} = 1.7$ μ M).

The galanin receptor is thought to be a target for the development of compounds for eating disorders.

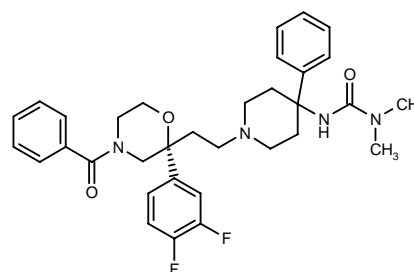
SOURCE – Schering-Plough.

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SR-144190**256855**

(+)-(*R*)-*N*-[1-[2-[4-Benzoyl-2-(3,4-difluorophenyl)morpholin-2-yl]ethyl]-4-phenylpiperidin-4-yl]-*N*',*N*'-dimethylurea



C33-H38-F2-N4-O3; Mol wt: 576.69

ACTION – Potent, selective, orally active, nonpeptide tachykinin NK₂ receptor antagonist shown to competitively antagonize [β -Ala⁸]-neurokinin A(4-10)-induced contractions of human bronchi ($pA_2 = 9.86$) and to inhibit [β -Ala⁸]-NKA(4-10)-induced contractions of human colonic circular smooth muscle strips ($pA_2 = 9.3 \pm 0.2$). *In vivo* in rats it antagonized [β -Ala⁸]-NKA(4-10)-induced urinary bladder contraction ($ID_{50} = 11 \mu\text{g/kg i.v.}, 190 \mu\text{g/kg i.d.}$) and castor oil-induced diarrhea ($0.01\text{--}10 \mu\text{g/kg s.c. or p.o.}$). In guinea pigs it blocked [Nle^{10}]-neurokinin A(4-10)-induced bronchoconstriction ($ID_{50} = 21 \mu\text{g/kg i.v.}, 250 \mu\text{g/kg i.d.}$) and prevented citric acid-induced cough and airways hyperresponsiveness to acetylcholine (1 mg/kg i.p.). In mice, it blocked [Nle^{10}]-NKA(4-10)-induced turning behavior ($ID_{50} = 3 \mu\text{g/kg i.v.}, 16 \mu\text{g/kg p.o.}$). It did not block the bronchoconstriction induced by histamine, 5-HT, acetylcholine or substance P. At 5 mg/kg i.v. it did not affect cardiac function, general hemodynamics or respiratory function in anesthetized dogs. After oral administration it has long-lasting effects and has increased CNS bioavailability as compared with SR-48968. Potentially useful as a tool for studying the role of NK₂ receptors in the CNS.

SOURCE – Sanofi.

REFERENCES

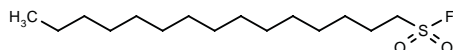
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ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

256839

Pentadecylsulfonyl fluoride



C15-H31-F-O2-S; Mol wt: 294.47

ACTION – Agent for the treatment of pain, nausea and glaucoma, as well as for preventing transplant organ rejection and as an appetite enhancer, that acts by inhibiting anandamide amidase, thus resulting in indirect stimulation of cannabinoid CB₁ and CB₂ receptors by increasing anandamide levels *in vivo*. By virtue of its indirect stimulatory activity, compound is expected to be devoid of the addictive and psychotropic properties of cannabinoids. *In vitro*, compound inhibited rat brain anandamide amidase with an IC₅₀ value of 7 nM and it was found to inhibit the degradation of anandamide at nanomolar concentrations in intact neuroblastoma N18TG2 cells. Compound was found to possess low binding affinity for the CB₁ receptor, being about 10-fold less potent than anandamide, while exhibiting 3-fold more potent antinociceptive activity than anandamide in the tail flick test in mice following i.v. administration.

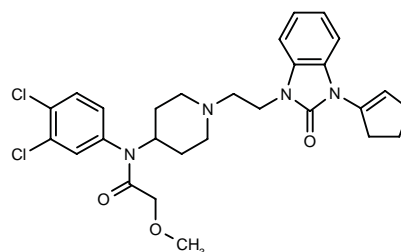
SOURCE – Univ. Connecticut, Storrs, CN (US).

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258376

N-[1-[2-[3-(1-Cyclopentenyl)-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl]ethyl]-4-piperidiny]-*N*-(3,4-dichlorophenyl)-2-methoxyacetamide



C28-H32-Cl2-N4-O3; Mol wt: 543.49

M.p. 144-5 °C.

ACTION – Orally active neurokinin receptor antagonist with strong affinity and selectivity for NK₁ receptors (K_i = 0.25 nM using human receptors; pA₂ = 9.4 in rabbit vena cava) versus NK₂ (K_i = 2000 nM using human receptors) and NK₃ receptors (pA₂ = 5.75-6.73 in rat portal vein); it also shows low affinity for the μ-opioid receptor (K_i = 2800 nM in rat brain membranes). Analgesic activity was demonstrated in the hot-plate test in mice (ED₅₀ = 0.4 mg/kg i.v.; ED₅₀ morphine = 0.3 mg/kg i.v.) The compound also inhibited substance P-induced bronchoconstriction in guinea pigs (ID₅₀ approx. 3 mg/kg p.o.; 29, 70 and 89% inhibition at 0.03, 0.1 and 1 mg/kg i.v., respectively). Potentially useful in the treatment of pain and inflammatory disorders, particularly of the pulmonary system (asthma).

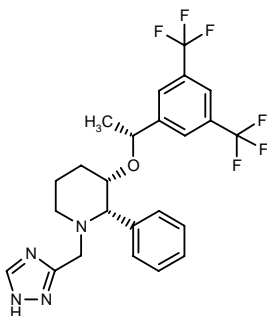
SOURCE – Servier.

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258380

(2*S*,3*S*)-3-[1(*R*)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-2-phenyl-1-(1*H*-1,2,4-triazol-3-ylmethyl)piperidine



C24-H24-F6-N4-O; Mol wt: 498.47

ACTION – Tachykinin NK₁ receptor antagonist, a 3-benzyloxy-2-phenylpiperidine derivative with high affinity for the receptor (IC₅₀ = 0.16 nM). It displayed potent activity and a relatively long duration of action in antagonizing resiniferatoxin-induced plasma extravasation *in vivo* (ID₅₀ = 0.06 mg/kg p.o. at 1 h; 78 and 12% inhibition at 8 and 24 h, respectively, after 1 mg/kg p.o.).

SOURCES – Merck & Co.; Merck Sharp & Dohme.

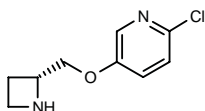
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ABT-594

258695

(*R*)-2-Chloro-5-(2-azetidylmethoxy)pyridine



C9-H11-Cl-N2-O; Mol wt: 198.65

ACTION – Potential analgesic agent, a potent neuronal nicotinic acetylcholine receptor (nAChR) positive modulator with high affinity and selectivity for α4β2 neuronal nAChR (K_i = 0.037 nM) and very low affinity for neuromuscular acetylcholine receptors (K_i > 10,000 nM). Preclinical studies in various models of pain (acute thermal, persistent chemical and neuropathic pain) showed that ABT-594 had both peripheral and central antinociceptive effects with a reduced cardiovascular liability compared to other nAChR ligands, and it was apparently devoid of opioid-like withdrawal effects. It appears to selectively modulate pain transmission by inhibiting substance P release from C fibers and by activating brainstem descending pain-inhibitory systems.

SOURCE – Abbott.

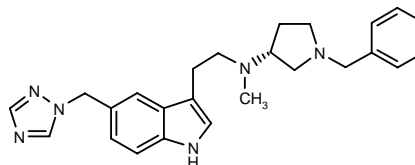
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ANTIMIGRAINE DRUGS

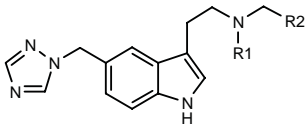
257809

1-Benzyl-3(*R*)-[*N*-methyl-*N*-[2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethyl]amino]pyrrolidine

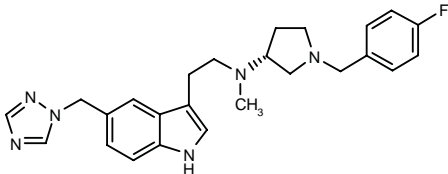


C25-H30-N6; Mol wt: 414.55

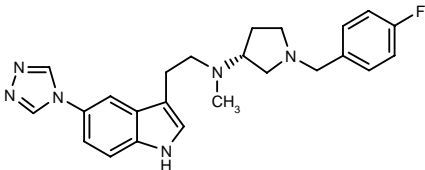
ACTION – Antimigraine agent, a potent 5-HT_{1D} receptor agonist with at least 10-fold greater affinity for the human 5-HT_{1Dα} (5-HT_{1D}) receptor subtype relative to the 5-HT_{1Dβ} (5-HT_{1B}) subtype, and thus expected to be associated with fewer side effects, particularly cardiovascular effects, compared to non-subtype-selective 5-HT_{1D} agonists. Other specifically claimed azetidine, pyrrolidine and piperidine derivatives include the following:



Compound	R1	R2	Formula
258927	Et	1-(PhCH2)-4-azetidiny	C ₂₆ H ₃₂ N ₆
258928	Me	1-(2-Cl-PhCH2)-4-azetidiny	C ₂₅ H ₂₉ ClN ₆
258929	Me	1-(PhCH2)-4-OH-4-azetidiny	C ₂₅ H ₃₀ N ₆ O
258930	Me	1-(cyclohexyl-CH2)-3-Pip	C ₂₇ H ₄₀ N ₆



258931: C25-H29-F-N6



258932: C24-H27-F-N6

SOURCE – Merck Sharp & Dohme.

REFERENCES

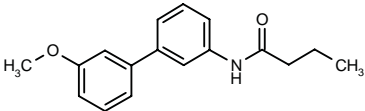
1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme, Ltd.) *Azetidine, pyrrolidine and piperidine derivs. as 5-HT receptor agonists.* WO 9742189.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

257232

N-(3'-Methoxybiphenyl-3-yl)butyramide



C17-H19-N-O2; Mol wt: 269.34

ACTION – Agent for the treatment of sleep and chronobiological disorders that acts by virtue of its melatonergic activity; it displaced 2-[¹²⁵I]-iodomelatonin binding from human MEL_{1A} receptors with an IC₅₀ < 100 nM.

SOURCE – Bristol-Myers Squibb.

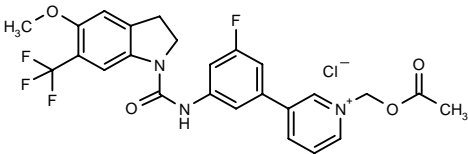
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ANXIOLYTICS

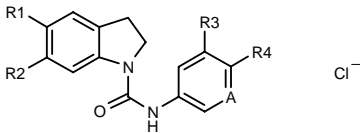
257217

1-(Acetoxymethyl)-3-[3-fluoro-5-[5-methoxy-6-(trifluoromethyl)indolin-1-ylcarboxamido]phenyl]pyridinium chloride



C25-H22-Cl-F4-N3-O4; Mol wt: 539.91

ACTION – Prodrug of a known 5-HT_{2C} receptor antagonist with increased solubility and increased *in vivo* activity as compared to the parent compound, potentially useful in the treatment of CNS disorders such as anxiety, depression and schizophrenia. Other specifically claimed indole derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
258319	OMe	CF3	1-(AcOCH2)-3-Pyr	Me	C(F)	C ₂₆ H ₂₄ ClF ₄ N ₃ O ₄
258320	Cl	Cl	H	1-(AcOCH2)-2-Me-3-Pyr-O	N	C ₂₃ H ₂₁ Cl ₃ N ₄ O ₄
258321	OMe	CF3	1-(AcOCH2)-3-Pyr	F	C(F)	C ₂₅ H ₂₁ ClF ₅ N ₃ O ₄

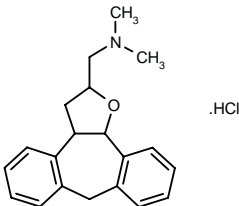
SOURCE – SmithKline Beecham.

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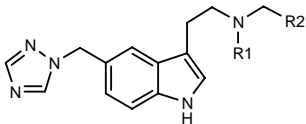
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257252

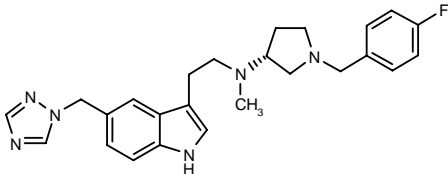
(±)-N,N-Dimethyl-N-(3,3a,8,12b-tetrahydro-2H-dibenzo[3,4:6,7]cyclohepta[1,2-b]furan-2-ylmethyl)amine hydrochloride



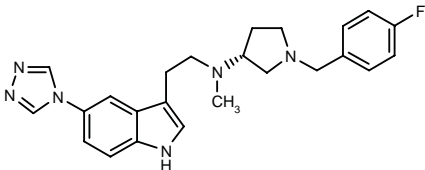
C20-H23-N-O.HCl; Mol wt: 329.87



Compound	R1	R2	Formula
258927	Et	1-(PhCH2)-4-azetidiny	C ₂₆ H ₃₂ N ₆
258928	Me	1-(2-Cl-PhCH2)-4-azetidiny	C ₂₅ H ₂₉ ClN ₆
258929	Me	1-(PhCH2)-4-OH-4-azetidiny	C ₂₅ H ₃₀ N ₆ O
258930	Me	1-(cyclohexyl-CH2)-3-Pip	C ₂₇ H ₄₀ N ₆



258931: C25-H29-F-N6



258932: C24-H27-F-N6

SOURCE – Merck Sharp & Dohme.

REFERENCES

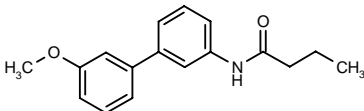
1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme, Ltd.) *Azetidine, pyrrolidine and piperidine derivs. as 5-HT receptor agonists.* WO 9742189.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

257232

N-(3'-Methoxybiphenyl-3-yl)butyramide



C17-H19-N-O2; Mol wt: 269.34

ACTION – Agent for the treatment of sleep and chronobiological disorders that acts by virtue of its melatonergic activity; it displaced 2-[¹²⁵I]-iodomelatonin binding from human MEL_{1A} receptors with an IC₅₀ < 100 nM.

SOURCE – Bristol-Myers Squibb.

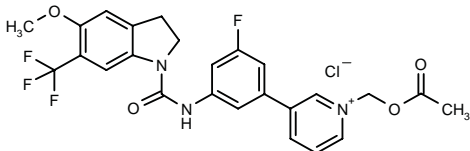
REFERENCES

1. Epperson, J.R. and Yevich, J.P. (Bristol-Myers Squibb Co.) *Biphenylamido derivs. as melatonergic agents.* WO 9738682.

ANXIOLYTICS

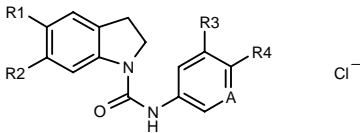
257217

1-(Acetoxymethyl)-3-[3-fluoro-5-[5-methoxy-6-(trifluoromethyl)indolin-1-ylcarboxamido]phenyl]pyridinium chloride



C25-H22-Cl-F4-N3-O4; Mol wt: 539.91

ACTION – Prodrug of a known 5-HT_{2C} receptor antagonist with increased solubility and increased *in vivo* activity as compared to the parent compound, potentially useful in the treatment of CNS disorders such as anxiety, depression and schizophrenia. Other specifically claimed indole derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
258319	OMe	CF3	1-(AcOCH2)-3-Pyr	Me	C(F)	C ₂₆ H ₂₄ ClF ₄ N ₃ O ₄
258320	Cl	Cl	H	1-(AcOCH2)-2-Me-3-Pyr-O	N	C ₂₃ H ₂₁ Cl ₃ N ₄ O ₄
258321	OMe	CF3	1-(AcOCH2)-3-Pyr	F	C(F)	C ₂₅ H ₂₁ ClF ₅ N ₃ O ₄

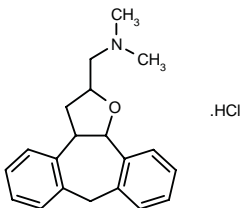
SOURCE – SmithKline Beecham.

REFERENCES

1. Bromidge, S.M. (SmithKline Beecham) *Indole derivs. as 5-HT receptor antagonist.* WO 9737989.

257252

(±)-N,N-Dimethyl-N-(3,3a,8,12b-tetrahydro-2H-dibenzo[3,4:6,7]cyclohepta[1,2-b]furan-2-ylmethyl)amine hydrochloride



C20-H23-N-O.HCl; Mol wt: 329.87

ACTION – Agent for the treatment of CNS disorders such as anxiety, depression and psychosis, cardiovascular and gastrointestinal disorders and migraine with affinity for 5-HT_{2A} and 5-HT_{2C} receptors, as demonstrated in binding assays (> 40% inhibition of [³H]-ketanserin and [³H]-mesulergine binding in rat frontal cortex and pig choroid plexus, respectively, at 0.1 μM). *In vivo*, compound was found to suppress mCPP-induced hypolocomotion in rats at a dose of 2.5 mg/kg or less.

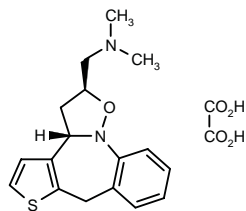
SOURCE – Janssen.

REFERENCES

1. Gil-Lopetegui, P. et al. (Janssen Pharm. NV) *Substd. tetracyclic tetrahydrofuran derivs.* WO 9738991.

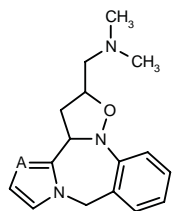
257259

(±)-*cis*-*N,N*-Dimethyl-*N*-(2,3,3a,7-tetrahydroisoxazolo[2,3-*a*]thieno[3,2-*c*][1]benzazepin-2-ylmethyl)amine oxalate

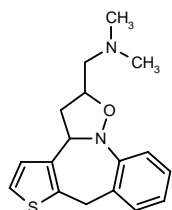


C17-H20-N2-O-S.C2-H2-O4; Mol wt: 390.45

ACTION – Agent for the treatment of anxiety, depression, schizophrenia, migraine and drug addiction with affinity for 5-HT₂ receptors, particularly 5-HT_{2A} and 5-HT_{2C} receptors (> 40% inhibition of [³H]-ketanserin binding in rat frontal cortex preparations [5-HT_{2A}] and [³H]-mesulergine binding in pig choroid plexus preparations [5-HT_{2C}] at 0.1 μM). *In vivo*, activity was demonstrated in the mCPP test in rats and in the plus maze test in rats. Other specifically claimed isoxazolidine derivatives include the following:



Compound	A	Formula
258650	CH	C ₁₇ H ₂₁ N ₃ O
258651	N	C ₁₆ H ₂₀ N ₄ O



258652: C17-H20-N2-O-S

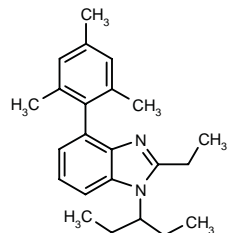
SOURCE – Janssen.

REFERENCES

1. Andrs-Gil, I. et al. (Janssen Pharm. NV) *Isoxazolidine derivs.* WO 9739001.

258729

2-Ethyl-1-(1-ethylpropyl)-4-(2,4,6-trimethylphenyl)benzimidazole



C23-H30-N2; Mol wt: 334.50

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of a wide range of stress-related disorders such as anxiety, depression, headache, irritable bowel syndrome, inflammatory disorders, Alzheimer's disease, gastrointestinal disorders, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, infertility, stroke and stress-induced infections.

SOURCE – Pfizer.

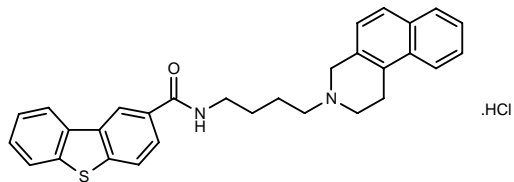
REFERENCES

1. Volkmann, R.A. (Pfizer, Inc.) *Benzimidazole derivs. and their use as corticotropin releasing factor antagonists.* EP 812831.

ANTIPSYCHOTIC DRUGS

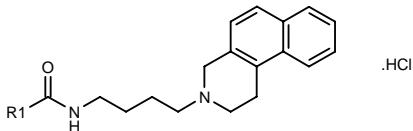
256843

N-[4-(1,2,3,4-Tetrahydrobenz[*f*]isoquinolin-3-yl)butyl]-dibenzothiophene-2-carboxamide hydrochloride

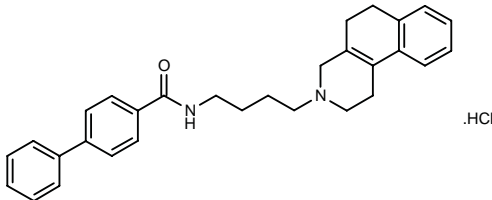


C30-H28-N2-O-S.HCl; Mol wt: 501.08

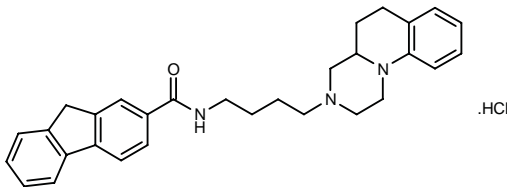
ACTION – Agent for the treatment or prevention of neuropsychological disorders such as schizophrenia, mania, depression, anxiety, Alzheimer's disease, dementia, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson's disease and motor disorders related to the use of neuroleptic agents that exhibits high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors (K_i = 5 and 377 nM, respectively, for displacement of [³H]-YM-09151-2 binding to recombinant monkey D₃ and D₂ receptors expressed in COS cells). A representative compound from a series of specifically claimed tricyclic aminoalkylcarboxamides, wherein the following are also included:



Compound	R1	Formula
258134	3-quinolinyl	C ₂₇ H ₂₇ N ₃ O.HCl
258135	2-quinoxaliny	C ₂₆ H ₂₆ N ₄ O.HCl



258136: C30-H32-N2-O.HCl



258137: C30-H33-N3-O.HCl

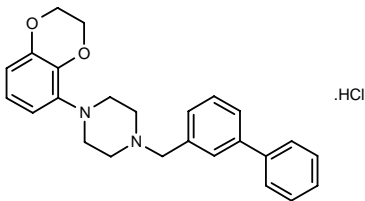
SOURCE – Neurogen.

REFERENCES

1. Chen, X. et al. (Neurogen Corp.) *Tricyclic aminoalkylcarboxamides; novel dopamine D₃ receptor. subtype specific ligands.* US 5688950, WO 9740015.

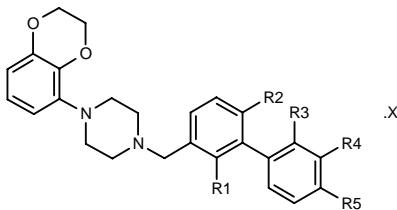
257174

1-(Biphenyl-3-methyl)-4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine hydrochloride



C25-H26-N2-O2.HCl; Mol wt: 422.95

ACTION – Antipsychotic agent with high affinity for dopamine D₂ and 5-HT_{1A} receptors, expected to induce less extrapyramidal side effects than available antipsychotic drugs due to its low propensity to induce catalepsy in rodents. Other compounds from this series of piperazine and piperidine derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
258138	OH	H	H	H	H		C ₂₅ H ₂₆ N ₂ O ₃
258139	H	H	H	OMe	H	HCl	C ₂₆ H ₂₈ N ₂ O ₃ .HCl
258140	H	H	CN	H	H	HCl	C ₂₆ H ₂₅ N ₃ O ₂ .HCl
258141	H	OH	H	H	F	HCl	C ₂₅ H ₂₅ FN ₂ O ₃ .HCl

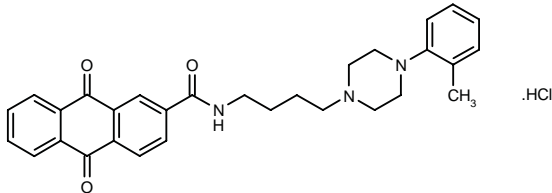
SOURCE – Duphar.

REFERENCES

1. Feenstra, R.W. et al. (Duphar Int. Res. B.V.) *Piperazine and piperidine cpds.* WO 9736893.

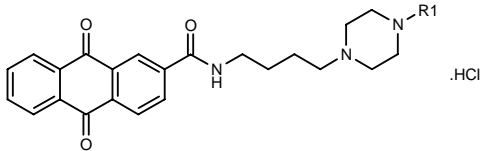
257250

N-[4-[4-(2-Methylphenyl)piperazin-1-yl]butyl]anthraquinone-2-carboxamide hydrochloride



C30-H31-N3-O3.HCl; Mol wt: 518.05

ACTION – Agent for the treatment or prevention of neuropsychological disorders such as schizophrenia, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson’s disease and motor disorders related to the use of neuroleptic agents that exhibits high affinity and selectivity for the dopamine D₃ receptor over the D₂ receptor (K_i = 1 and 106 nM, respectively, for displacement of [³H]-YM-09151-2 binding to monkey D₃ and D₂ receptors expressed in COS cells). A representative compound from a series of specifically claimed N-aminoalkyl-2-anthraquinonecarboxamides, wherein the following are also included:



Compound	R1	Formula
258565	2,3-(Cl)2-Ph	C ₂₉ H ₂₇ Cl ₂ N ₃ O ₃ .HCl
258566	1-Naph	C ₃₃ H ₃₁ N ₃ O ₃ .HCl
258567	2,3-(Me)2-Ph	C ₃₁ H ₃₃ N ₃ O ₃ .HCl
258568	3-Cl-2-Me-Ph	C ₃₀ H ₃₀ ClN ₃ O ₃ .HCl
258569	8-quinolinyl	C ₃₂ H ₃₀ N ₄ O ₃ .HCl
258570	2-MeO-Ph	C ₃₀ H ₃₁ N ₃ O ₄ .HCl

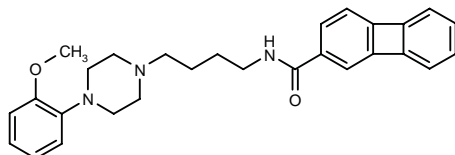
SOURCE – Neurogen.

REFERENCES

1. Chen, X. and Wasley, J.W.F. (Neurogen Corp.) *N-Aminoalkyl-2-anthraquinonecarboxamides; new dopamine receptor subtype specific ligands*. US 5703237, WO 9738989.

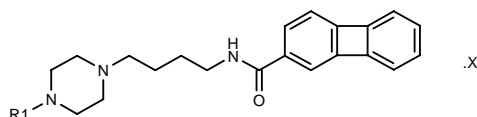
257251

N-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]biphenylene-2-carboxamide

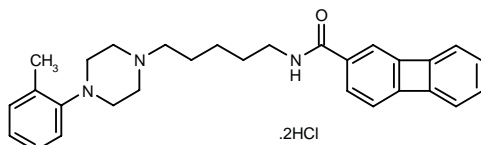


C28-H31-N3-O2; Mol wt: 441.57

ACTION – Agent for the treatment and prevention of neuropsychological disorders such as schizophrenia, mania, depression, anxiety, Alzheimer's disease, dementia, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson's disease and motor disorders related to the use of neuroleptic agents that exhibits high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors (K_i = 5 and 323 nM, respectively, for inhibition of [³H]-YM-09151-2 binding to recombinant monkey D₃ and D₂ receptors expressed in COS cells). Other compounds from this series of specifically claimed *N*-aminoalkyl-1-biphenylenyl-2-carboxamides include the following:



Compound	R1	X	Formula
258808	2,3-(Me)2-Ph	2HCl	C ₂₉ H ₃₃ N ₃ O.2HCl
258809	1-Naph	2HCl	C ₃₁ H ₃₁ N ₃ O.2HCl
258810	1-isoquinolyl	2HCl	C ₃₀ H ₃₀ N ₄ O.2HCl
258811	1-indanyl	2HCl	C ₃₀ H ₃₃ N ₃ O.2HCl
258812	8-quinoliny		C ₃₀ H ₃₀ N ₄ O
258813	2-Cl-Ph		C ₂₇ H ₂₆ ClN ₃ O
258814	2,3-(Cl)2-Ph		C ₂₇ H ₂₇ Cl ₂ N ₃ O
258815	2,6-(Me)2-Ph	2HCl	C ₂₉ H ₃₃ N ₃ O.2HCl
258816	2,6-(Cl)2-Ph		C ₂₇ H ₂₇ Cl ₂ N ₃ O



258819: C29-H33-N3-O.2HCl

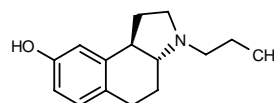
SOURCE – Neurogen.

REFERENCES

1. Chen, X. and Yuan, J. (Neurogen Corp.) *Novel N-aminoalkyl-1-biphenylenyl-2-carboxamides; new dopamine receptor subtype specific ligands*. WO 9738990.

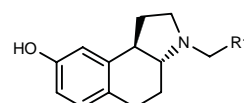
257760

(+)-*trans*-3-Propyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[e]indol-8-ol



C15-H21-N-O; Mol wt: 231.34

ACTION – Agent for the treatment of CNS disorders such as schizophrenia, Parkinson's disease, depression, drug abuse, pain, neurodegenerative disorders and eating disorders with high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors. Other specifically claimed enantiomers of *trans*-benz[e]indole compounds include the following:



Compound	R1	Isomer	Formula
259224	Et	(-)	C ₁₅ H ₂₁ NO
259225	vinyl	(+)	C ₁₅ H ₁₉ NO
259226	vinyl	(-)	C ₁₅ H ₁₉ NO

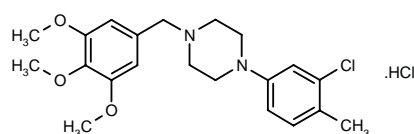
SOURCE – Novo Nordisk.

REFERENCES

1. Scheidele, M. et al. (Novo Nordisk A/S) *Enantiomers of trans-benz[e]indole cpds., their preparation and utility as dopamine-D3 receptor selective agents*. WO 9741101.

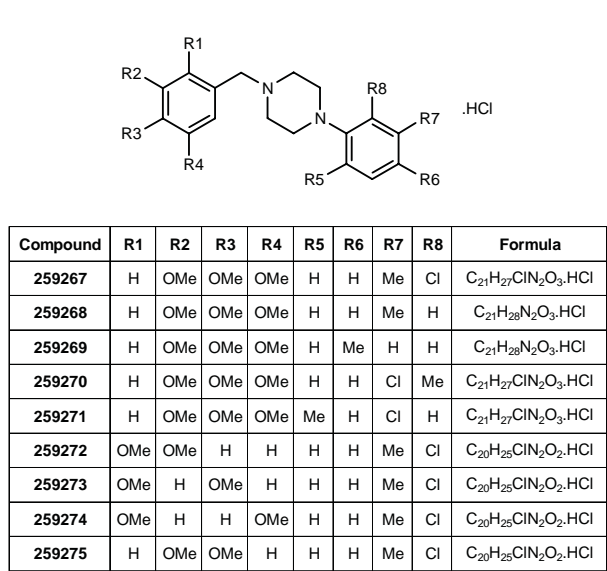
257764

1-(3-Chloro-4-methylphenyl)-4-(3,4,5-trimethoxybenzyl)-piperazine hydrochloride



C21-H27-Cl-N2-O3.HCl; Mol wt: 427.37

ACTION – Atypical antipsychotic agent, a potent and selective dopamine D₄ receptor antagonist, as demonstrated in binding assays (K_i = 4.5 nM for human D₄ receptors vs. 3290 and 2025 nM, respectively, for human D₂ and D₃ receptors), expected to be free of extrapyramidal side effects due to its high D₄ selectivity. Within this series of specifically claimed substituted piperazines and piperidines, the following are also included:



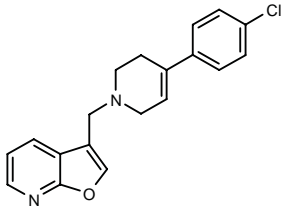
SOURCE – Warner-Lambert.

REFERENCES

1. Glase, S.A. et al. (Warner-Lambert Co.) *Substd. piperazines and piperidines as central nervous system agents*. WO 9741108.

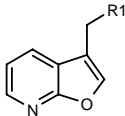
258210

3-[4-(4-Chlorophenyl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]furo[2,3-*b*]pyridine



C19-H17-Cl-N2-O; Mol wt: 324.81

ACTION – Antipsychotic agent and antidepressant with potent affinity for dopamine D₄ receptors (K_i < 1.5 μM against [³H]-spiperone binding to human D₄ receptors expressed in clonal cell lines). Other specifically claimed compounds from this series of furo[2,3-*b*]pyridine derivatives include the following:



Compound	R1	Formula
258285	(E)-4-(PhCH=CH)-1,2,3,6-tetrahydro-1-Pyr	C ₂₁ H ₂₀ N ₂ O
258286	4-(4-Cl-Ph)-1-Piz	C ₁₈ H ₁₈ ClN ₃ O

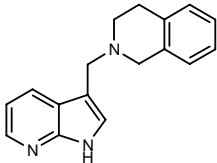
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Curtis, N.R. et al. (Merck Sharp & Dohme, Ltd.) *Europyridine derivs*. US 5700802.

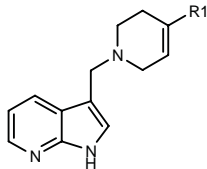
258211

3-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)-1 *H*-pyrrolo[2,3-*b*]pyridine

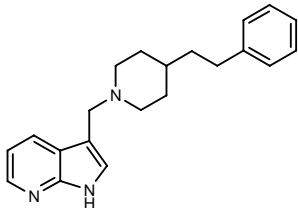


C17-H17-N3; Mol wt: 263.34

ACTION – Antipsychotic agent that selectively binds to the dopamine D₄ receptor (K_i < 1.5 μM against [³H]-spiperone binding to human D₄ receptors expressed in clonal cell lines). A representative compound from a series of specifically claimed pyrrolo[2,3-*b*]pyridine derivatives, wherein the following are also included:



Compound	R1	Formula
258288	Ph	C ₁₉ H ₁₉ N ₃
258289	CH=CHPh	C ₂₁ H ₂₁ N ₃
258290	CH2CH2Ph	C ₂₁ H ₂₃ N ₃
258291	2-Naph	C ₂₃ H ₂₁ N ₃
258292	4-MeO-Ph	C ₂₀ H ₂₁ N ₃ O



258287: C21-H25-N3

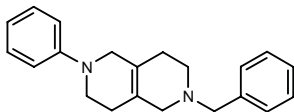
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Leeson, P.D. et al. (Merck Sharp & Dohme, Ltd.) *Pyrrolo-pyridine derivs*. US 5700809, WO 9420459.

258214

2-Benzyl-6-phenyl-1,2,3,4,5,6,7,8-octahydro-2,6-naphthyridine



C21-H24-N2; Mol wt: 304.43

ACTION – Antipsychotic agent and antidepressant, a dopamine D₄ receptor ligand (K_i < 1.5 μM against [³H]-spiperone binding to human D₄ receptors expressed in clonal cell lines).

SOURCE – Merck Sharp & Dohme.

REFERENCES

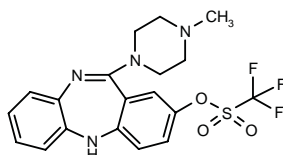
1. Kulagowski, J.J. (Merck Sharp & Dohme, Ltd.) *Octahydronaphthyridine derivs.* US 5700941.

GMC1-169*

242168

11-(4-Methylpiperazin-1-yl)-2-(trifluoromethanesulfonyloxy)-5*H*-dibenzo[*b,e*][1,4]diazepine

Trifluoromethanesulfonic acid 11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl ester



C19-H19-F3-N4-O3-S; Mol wt: 440.44

M.p. 160 °C.

ACTION – Atypical antipsychotic agent, a triflate-substituted analog of clozapine acting on a wide range of CNS receptors similar to clozapine, mostly at 5-HT_{2A} (IC₅₀ = 8 nM for inhibition of [³H]-ketanserin binding in rat brain membranes) and 5-HT_{2C} (IC₅₀ = 34 nM for inhibition of [³H]-mesulergine binding to cloned rat receptors expressed in 3T3 cells) and dopamine D₁ and D₂ receptors (IC₅₀ = 64 nM for inhibition of [³H]-Sch-23390 and 31 nM for inhibition of [³H]-spiperone binding in rat corpus striatum membranes, respectively), as well as α₁-adrenoceptors (IC₅₀ = 12 nM for inhibition of [³H]-prazosin binding in rat brain membranes) and histamine H₁ receptors (IC₅₀ = 47 nM for inhibition of [³H]-mepyramine binding in rat brain membranes), but presenting no significant affinity for muscarinic receptors. In behavioral studies, GMC-1-169 did not induce catalepsy even at doses that blocked apomorphine-induced hyperactivity.

SOURCE – Lundbeck.

REFERENCES

1. De Boer, P. and Liao, Y. (Håkan Wikström) *New sulfone ester analogues of iso-clozapine and related structures: Atypical neuroleptics.* WO 9629316.

2. Alves-Rodrigues, A. et al. *Binding of clozapine metabolites and analogues to the histamine H₃ receptor in rat brain cortex.* Arch Pharm Pharm Med Chem 1996, 329(8-9): 413.

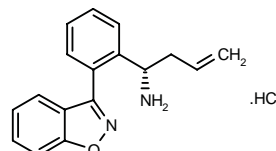
3. Liao, Y. et al. *Synthesis and pharmacological evaluation of triflate-substituted analogues of clozapine: Identification of a novel atypical neuroleptic.* J Med Chem 1997, 40(25): 4146.

*Identified compound **242168** Drug Data Rep 1997, 19(2): 114.

ANTIDEPRESSANTS

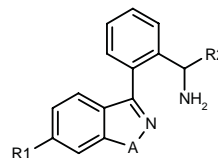
257720

(-)-(S)-1-[2-(3-Benzisoxazolyl)phenyl]-3-butenylamine hydrochloride



C17-H16-N2-O.HCl; Mol wt: 300.79

ACTION – Antidepressant found to suppress REM sleep in rats at doses ranging from 0.1 to 1 mg/kg i.p., with a potency higher than that of reference compounds such as amitriptyline, imipramine, venlafaxine, fluvoxamine and moclobemide. Compound was also tested in the mouse marble-burying assay, giving an ED₅₀ of 0.39 mg/kg s.c. Also claimed for the treatment of anxiety, eating disorders, sleep disorders, schizophrenia and sexual function disorders. Other specifically claimed substituted benzylamines include the following:



Compound	R1	R2	A	Isomer	Formula
258641	H	H	O		C ₁₄ H ₁₂ N ₂ O
258642	H	allyl	O		C ₁₇ H ₁₆ N ₂ O
258643	H	allyl	O	(+)-R	C ₁₇ H ₁₆ N ₂ O
258644	H	Bu	O		C ₁₈ H ₂₀ N ₂ O
258645	H	ethynyl-CH ₂	O		C ₁₇ H ₁₄ N ₂ O
258646	H	allyl	N(Me)		C ₁₈ H ₁₉ N ₃
258647	Cl	ethynyl-CH ₂	O	(-)	C ₁₇ H ₁₃ ClN ₂ O
258648	Cl	allyl	O	(-)-S	C ₁₇ H ₁₅ ClN ₂ O

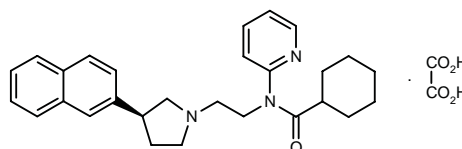
SOURCE – Akzo Nobel.

REFERENCES

1. Leysen, D.C.M. et al. (Akzo Nobel NV) *Subst. benzylamines and their use for the treatment of depression.* WO 9740027.

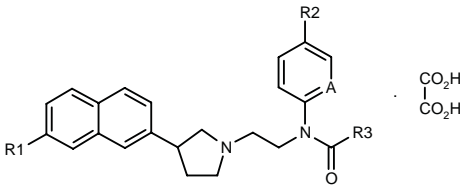
257728

(-)-N-[2-[3(S)-(2-Naphthyl)pyrrolidin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide oxalate

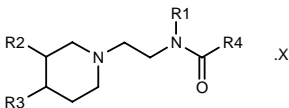


C28-H33-N3-O.C2-H2-O4; Mol wt: 517.62

ACTION – Antidepressant, a 5HT_{1A} receptor antagonist (IC₅₀ = 9 nM) that also has marked 5-HT reuptake-inhibitory activity (IC₅₀ = 1 nM). Other specifically claimed piperidines and pyrrolidines include the following:



Compound	R1	R2	R3	A	Isomer	Formula
258660	H	H	cyclohexyl	N		C ₂₈ H ₃₃ N ₃ O .C ₂ H ₂ O ₄
258661	H	H	cyclohexyl	N	R	C ₂₈ H ₃₃ N ₃ O .C ₂ H ₂ O ₄
258665	H	F	1-adamantyl	CH		C ₃₃ H ₃₇ FN ₂ O .C ₂ H ₂ O ₄
258667	OMe	H	cyclohexyl	N		C ₂₉ H ₃₅ N ₃ O ₂ .C ₂ H ₂ O ₄



Compound	R1	R2	R3	R4	X	Formula
258659	2-Pyr	H	6-F-3-indolyl	cyclohexyl-NH		C ₂₇ H ₃₄ FN ₅ O
258662	2-Pyr	2-Naph	H	cyclohexyl	oxalate	C ₂₉ H ₃₅ N ₃ O .C ₂ H ₂ O ₄
258663	2-Pyr	H	5-F-3-indolyl	cyclohexyl		C ₂₇ H ₃₃ FN ₄ O
258664	2-Pyr	H	6-F-3-indolyl	cyclohexyl	oxalate	C ₂₇ H ₃₃ FN ₄ O .C ₂ H ₂ O ₄
258666	2,4-(F)2-Ph	H	6-F-3-indolyl	cyclohexyl-NH		C ₂₈ H ₃₃ F ₃ N ₄ O

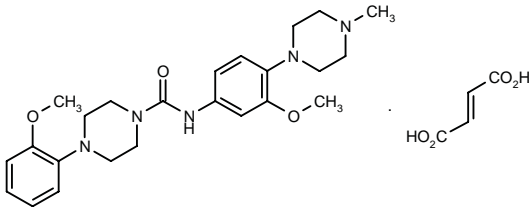
SOURCE – Merck KGaA.

REFERENCES

1. März, J. et al. (Merck Patent GmbH) *Piperidines and pyrrolidines*. DE 19615232, WO 9740038.

258686

N-[3-Methoxy-4-(4-methylpiperazin-1-yl)phenyl]-4-(2-methoxyphenyl)piperazine-1-carboxamide fumarate



C24-H33-N5-O3.C4-H4-O4; Mol wt: 555.63

ACTION – Potent, selective and orally active 5-HT_{1B} receptor antagonist (K_i = 2.0, 700 and 90 nM for cloned human 5-HT_{1B}, 5-HT_{1A} and 5-HT_{1D} receptors, respectively; K_B = 16 nM for antagonism of 5-CT-induced inhibition of cAMP formation in human 5-HT_{1B} receptor-expressing CHO-K1 cells), which can be classified as a silent antagonist since it does not show intrinsic activity at 5-HT_{1B} receptors *in vitro*. The compound shows 5-HT_{1B}-antagonist activity *in vivo* in reversing hypothermia induced by a 5-HT_{1B/1D} agonist in guinea pigs (ED₅₀ = 0.52 mg/kg i.p., 0.31 mg/kg p.o.). In addition, it induced an increase in ter-

минаl 5-HT release in the hypothalamus of guinea pigs after systemic administration (0.16 and 0.63 mg/kg i.p.), indicating antidepressant properties. Selected for further evaluation from a series of arylpiperazine derivatives of phenylpiperazines.

SOURCE – Pierre Fabre.

REFERENCES

1. Jorand-Lebrun, C. et al. *Arylpiperazine derivatives of phenylpiperazines as a new class of potent and selective 5-HT_{1B} receptor antagonists*. Bioorg Med Chem Lett 1997, 7(24): 3183.

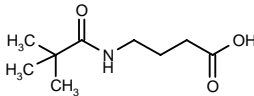
PIVAGABINE

Rec INN

186739

4-Pivalamidobutyric acid

4-(2,2-Dimethylpropionamido)butanoic acid



C9-H17-N-O3; Mol wt: 187.24

ACTION – Psychoactive compound with anxiolytic and antidepressant properties that acts by modulating hypothalamic release of corticotropin-releasing factor (CRF) and by antagonizing the activation of CRF induced by stress. Pivagabine was shown to improve anxiety and depression in patients with climacteric syndrome. The efficacy of pivagabine was also assessed for the management of “distress” in children hospitalized for acute diseases, in whom the treatment clearly improved behavior and motor function, as well as attention and sleep. The compound has also proven effective in patients with insomnia associated with mood disorders, neurasthenia, dysthymic disorders and elderly patients with adjustment disorders. Pivagabine is rapidly absorbed through the gastrointestinal tract, with complete oral bioavailability, and easily penetrates the blood–brain barrier.

INDICATION – Treatment of depressive syndromes.

PRESENTATION – Granules, 900 mg.

PROPRIETARY NAME – Tonerg (IT).

SOURCE – Angelini.

REFERENCES

1. Bianchi, M. et al. *Pharmacokinetics and in vitro effects of a 4-aminobutyric acid derivative with anticonvulsant action*. Pharmacology 1983, 27(4): 237.

2. Esposito, G. and Luparimi, M.R. *Pivagabine: A novel psychoactive drug*. Arzneimittel-Forsch-Drug Res 1997, 47(11a): 1306.

3. Galzigna, L. et al. *Properties of two derivatives of gamma-aminobutyric acid (GABA) capable of abolishing cariazol- and bicuculline-induced convulsions in the rat*. Arch Int Pharmacodyn Ther 1978, 235(1): 73.

4. Gelsomini, S. *Use of pivagabine in the management of hospitalization distress in children*. Arzneimittel-Forsch-Drug Res 1997, 47(11a): 1332.

5. Gianni, A.M. et al. *Effect of pivagabine on stress-induced gastric ulcer formation in rats*. Arzneimittel-Forsch-Drug Res 1997, 47(11a): 1315.

6. Gigliotti, B. et al. *Role of pivagabine in the treatment of climacteric syndrome*. Arzneimittel-Forsch-Drug Res 1997, 47(11a): 1317.

7. Negri, L. *Evaluation of the efficacy of pivagabine on insomnia associated with mood disorders.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1322.

8. Pizzolato, G. et al. *Randomized, double-blind, placebo-controlled study of pivagabine in neurasthenia.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1329.

9. Scapagnini, U. and Matera, M. *Effects of pivagabine on psychophysical performance and behavioural response in experimental models of stress.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1310.

10. Terranova, R. et al. *Clinical evaluation of the efficacy of pivagabine in the treatment of mood and adjustment disorders.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1325.

11. *CRF modulator introduced in Italy.* *Prous Science Daily Essentials* July 4, 1997.

12. *New product intros.* *Drug News Perspect* 1997, 10(6): 360.

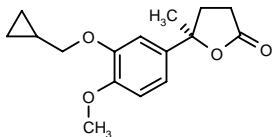
13. *Proposed international nonproprietary names (Prop. INN): List 66.* WHO Drug Inform 1991, 5(4): 203.

NEUROLOGIC DRUGS

TREATMENT OF IMMUNOLOGIC
NEUROMUSCULAR DISORDERS

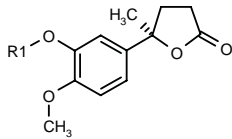
257724

(+)-(R)-5-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]-5-methyltetrahydrofuran-2-one



C16-H20-O4; Mol wt: 276.33

ACTION – Inhibitor of tumor necrosis factor-α (TNF-α) production and phosphodiesterase type IV (PDE IV) specifically claimed for the treatment of multiple sclerosis. Within this sereis of specifically claimed chiral phenyldihydrofuranones, the following are also included:



Compound	R1	Formula
258677	Pr	C ₁₅ H ₂₀ O ₄
258678	i-Bu	C ₁₆ H ₂₂ O ₄
258679	cyclobutyl	C ₁₆ H ₂₀ O ₄
258680	cyclopentyl	C ₁₇ H ₂₂ O ₄

SOURCE – Schering AG.

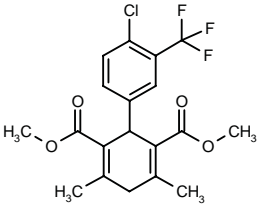
REFERENCES

1. Laurent, H. et al. (Schering AG) *Chiral phenyldihydrofuranones as PDE-IV inhibitors.* DE 19617864, WO 9740032.

COGNITION-ENHANCING DRUGS

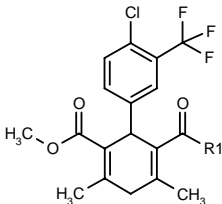
257146

4'-Chloro-3,5-dimethyl-3'-(trifluoromethyl)-1,4-dihydro-biphenyl-2,6-dicarboxylic acid dimethyl ester

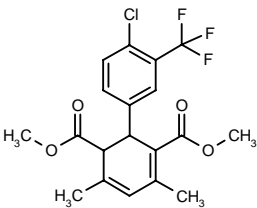


C19-H18-Cl-F3-O4; Mol wt: 402.80

ACTION – Agent for the treatment of CNS disorders including multiinfarct dementia, presenile and senile dementia of the Alzheimer's type and multiple sclerosis that acts by selectively modulating charybdotoxin-sensitive, calcium-dependent potassium (IK_{Ca}) channels. Within this series of dimethyl-substituted cyclohexane diene derivatives, the following are also included:



Compound	R1	Formula
257909	OH	C ₁₈ H ₁₆ ClF ₃ O ₄
257910	NH2	C ₁₈ H ₁₇ ClF ₃ NO ₃



257908: C19-H18-Cl-F3-O4

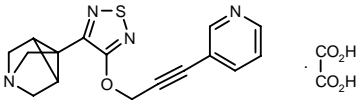
SOURCE – Bayer.

REFERENCES

1. Urbahns, K. and Mauler, F. (Bayer AG) *Dimethyl-substd. cyclohexane diene derivs.* WO 9736853.

257184

1-[4-[3-(3-Pyridyl)-2-propynyloxy]-1,2,5-thiadiazol-3-yl]-4-azatricyclo[2.2.1.0^{2,6}]heptane oxalate



C16-H14-N4-O-S.C2-H2-O4; Mol wt: 400.41

7. Negri, L. *Evaluation of the efficacy of pivagabine on insomnia associated with mood disorders.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1322.

8. Pizzolato, G. et al. *Randomized, double-blind, placebo-controlled study of pivagabine in neurasthenia.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1329.

9. Scapagnini, U. and Matera, M. *Effects of pivagabine on psychophysical performance and behavioural response in experimental models of stress.* *Arzneim-Forsch-Drug Res* 1997, 47(11a): 1310.

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11. *CRF modulator introduced in Italy.* *Prous Science Daily Essentials* July 4, 1997.

12. *New product intros.* *Drug News Perspect* 1997, 10(6): 360.

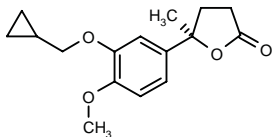
13. *Proposed international nonproprietary names (Prop. INN): List 66.* WHO Drug Inform 1991, 5(4): 203.

NEUROLOGIC DRUGS

TREATMENT OF IMMUNOLOGIC
NEUROMUSCULAR DISORDERS

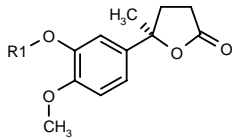
257724

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C16-H20-O4; Mol wt: 276.33

ACTION – Inhibitor of tumor necrosis factor- α (TNF- α) production and phosphodiesterase type IV (PDE IV) specifically claimed for the treatment of multiple sclerosis. Within this sereis of specifically claimed chiral phenyldihydrofuranones, the following are also included:



Compound	R1	Formula
258677	Pr	C ₁₅ H ₂₀ O ₄
258678	i-Bu	C ₁₆ H ₂₂ O ₄
258679	cyclobutyl	C ₁₆ H ₂₀ O ₄
258680	cyclopentyl	C ₁₇ H ₂₂ O ₄

SOURCE – Schering AG.

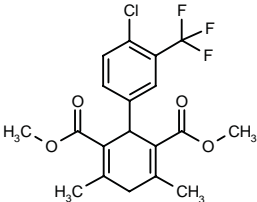
REFERENCES

1. Laurent, H. et al. (Schering AG) *Chiral phenyldihydrofuranones as PDE-IV inhibitors.* DE 19617864, WO 9740032.

COGNITION-ENHANCING DRUGS

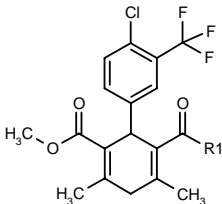
257146

4'-Chloro-3,5-dimethyl-3'-(trifluoromethyl)-1,4-dihydro-biphenyl-2,6-dicarboxylic acid dimethyl ester

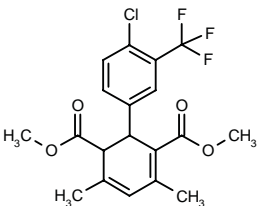


C19-H18-Cl-F3-O4; Mol wt: 402.80

ACTION – Agent for the treatment of CNS disorders including multiinfarct dementia, presenile and senile dementia of the Alzheimer's type and multiple sclerosis that acts by selectively modulating charybdotoxin-sensitive, calcium-dependent potassium (IK_{Ca}) channels. Within this series of dimethyl-substituted cyclohexane diene derivatives, the following are also included:



Compound	R1	Formula
257909	OH	C ₁₈ H ₁₆ ClF ₃ O ₄
257910	NH2	C ₁₈ H ₁₇ ClF ₃ NO ₃



257908: C19-H18-Cl-F3-O4

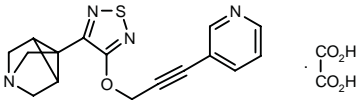
SOURCE – Bayer.

REFERENCES

1. Urbahns, K. and Mauler, F. (Bayer AG) *Dimethyl-substd. cyclohexane diene derivs.* WO 9736853.

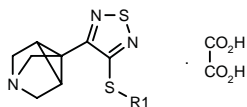
257184

1-[4-[3-(3-Pyridyl)-2-propynyloxy]-1,2,5-thiadiazol-3-yl]-4-azatricyclo[2.2.1.0^{2,6}]heptane oxalate

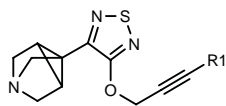


C16-H14-N4-O-S.C2-H2-O4; Mol wt: 400.41

ACTION – Agent for the treatment of senile dementia and Alzheimer's disease that modulates cholinergic muscarinic receptors. The affinity for muscarinic acetylcholine receptors was assessed by the ability to inhibit [³H]-Oxo-M binding in rat cortex preparations (IC_{50} = 6.0 nM), and it was shown to interact with the M_1 subtype, as demonstrated by inhibition of [³H]-pirenzepine binding in rat cortex preparations (IC_{50} = 400 nM). Within this series of specifically claimed azatricyclic compound, the following are also included:



Compound	R1	Formula
257996	Pr	C ₁₁ H ₁₅ N ₃ S ₂ ·C ₂ H ₂ O ₄
257997	CH ₂ CH ₂ CF ₃	C ₁₁ H ₁₂ F ₃ N ₃ S ₂ ·C ₂ H ₂ O ₄
257998	4-CN-Ph	C ₁₅ H ₁₂ N ₄ S ₂ ·C ₂ H ₂ O ₄



Compound	R1	X	Formula
257999	4-F-Ph	oxalate	C ₁₇ H ₁₄ FN ₃ OS ₂ ·C ₂ H ₂ O ₄
258000	Ph	oxalate	C ₁₇ H ₁₅ N ₃ OS ₂ ·C ₂ H ₂ O ₄
258001	3-thienyl	oxalate	C ₁₅ H ₁₃ N ₃ OS ₂ ·C ₂ H ₂ O ₄
258002	2-thienyl	oxalate	C ₁₅ H ₁₃ N ₃ OS ₂ ·C ₂ H ₂ O ₄
258003	3-MeO-Ph	HCl	C ₁₈ H ₁₇ N ₃ O ₂ S·HCl

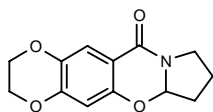
SOURCE – Novo Nordisk.

REFERENCES

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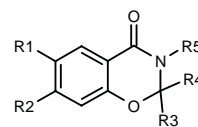
257185

2,3,6a,7,8,9-Hexahydro-11H-1,4-dioxino[2,3-g]pyrrolo-[2,1-b][1,3]benzoxazin-11-one



C₁₃-H₁₃-N-O₄; Mol wt: 247.25

ACTION – Agent that enhances synaptic responses mediated by AMPA receptors, potentially useful for facilitating learning and enhancing memory. *In vitro* activity was demonstrated by a concentration-dependent increase in the maximum amplitude and half-width of excitatory post-synaptic potentials (EPSPs) in rat hippocampus slices. *In vivo*, compound enhanced memory in rats tested in an 8-arm radial maze. Other representative compounds within this series of benzoxazines include the following:



Compound	R1	R2	R3	R4,R5	Formula
257989	-OCH ₂ O-		H	-(CH ₂) ₃ -	C ₁₂ H ₁₁ NO ₄
257990	-OCH ₂ O-		H	-(CH ₂) ₄ -	C ₁₃ H ₁₃ NO ₄
257991	H	OMe	H	-(CH ₂) ₃ -	C ₁₂ H ₁₃ NO ₃
257992	OMe	H	H	-(CH ₂) ₃ -	C ₁₂ H ₁₃ NO ₃
257993	-N=CHCH=N-		H	-(CH ₂) ₃ -	C ₁₃ H ₁₁ N ₃ O ₂
257994	-N=CHCH=N-		H	-(CH ₂) ₄ -	C ₁₄ H ₁₃ N ₃ O ₂
257995	OMe	H	Me	-(CH ₂) ₃ -	C ₁₃ H ₁₅ NO ₃

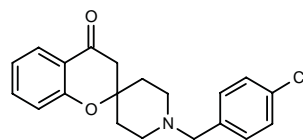
SOURCES – Univ. California, Oakland, CA (US); Cortex.

REFERENCES

1. Rogers, G.A. and Lynch, G.S. (Univ. California; Cortex Pharm., Inc.) *Benzoxazines for enhancing synaptic response* WO 9736907.

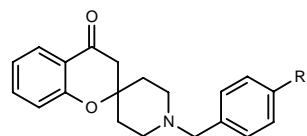
257190

1'-(4-Chlorobenzyl)-3,4-dihydrospiro[2H-1-benzopyran-2,4'-piperidin]-4-one



C₂₀-H₂₀-Cl-N-O₂; Mol wt: 341.84

ACTION – Agent for the treatment of cognitive disorders, as demonstrated by its ability to prevent diazepam-induced anterograde amnesia in mice (176% at 10 mg/kg p.o. administered 1 h before learning vs. 123% for vinpocetine at the same dose) and its ability to reverse electroshock-induced retrograde amnesia in mice (108% at 10 mg/kg p.o. administered 2 h after learning). In addition, it exerted 36% protection in the normobaric hypoxia-induced memory deficit model in rats at 10 mg/kg p.o., compared to 21% protection for vinpocetine at the same dose. It was found to inhibit neuronal calcium uptake, as measured by inhibition of potassium- and veratrine-induced uptake of ⁴⁵Ca²⁺ in synaptosome preparations (IC_{50} = 45.6 and 4.5 μ M, respectively). It was devoid of antiarrhythmic effects in rats with aconitine-induced arrhythmia. A representative compound from a series of specifically claimed spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one derivatives, wherein the following are also included:



Compound	R1	Formula
258250	F	C ₂₀ H ₂₀ FNO ₂
258251	Br	C ₂₀ H ₂₀ BrNO ₂
258252	NO ₂	C ₂₀ H ₂₀ N ₂ O ₄
258253	t-Bu	C ₂₄ H ₂₈ NO ₂

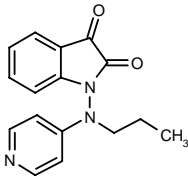
SOURCE – Gedeon Richter.

REFERENCES

1. Harsnyi, K. et al. (Richter Gedeon Vegyészeti Gyár RT) *Novel spiro[2H-1-benzopyran-2,4'-piperidine]-4(3H)-one derivs., acid addition salts thereof and pharmaceutical compsns. containing them.* WO 9737630.

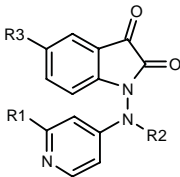
257254

1-[N-Propyl-N-(4-pyridyl)amino]indoline-2,3-dione



C16-H15-N3-O2; Mol wt: 281.31

ACTION – Agent for the treatment of cognition disorders by virtue of its acetylcholinesterase (AChE)-inhibitory activity. Compound is also reported to possess analgesic activity. Within this series of isatin derivatives, the following are also included:



Compound	R1	R2	R3	Formula
258820	H	H	H	C ₁₃ H ₉ N ₃ O ₂
258821	H	Me	OMe	C ₁₅ H ₁₃ N ₃ O ₃
258822	Cl	CH2CH2OH	H	C ₁₅ H ₁₂ ClN ₃ O ₃
258823	H	Et	OCONHMe	C ₁₇ H ₁₆ N ₄ O ₄
258824	H	Pr	OCON(Me)2	C ₁₉ H ₂₀ N ₄ O ₄
258825	H	Pr	1,2,3,4-tetrahydro-2-isquinolinyl-COO	C ₂₆ H ₂₄ N ₄ O ₄

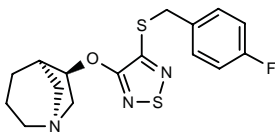
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Shimshock, S.J. et al. (Hoechst Marion Roussel, Inc.) *Isatin derivs. as acetylcholinesterase inhibitors and analgesics.* WO 9738993.

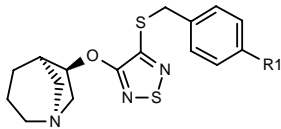
257709

(5*R*,6*R*)-endo-3-(1-Azabicyclo[3.2.1]oct-6-yloxy)-4-(4-fluorobenzylsulfanyl)-1,2,5-thiadiazole



C16-H18-F-N3-O-S2; Mol wt: 351.46

ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	Formula
258785	Me	C ₁₇ H ₂₁ N ₃ OS ₂
258786	Et	C ₁₈ H ₂₃ N ₃ OS ₂
258787	CF3	C ₁₇ H ₁₈ F ₃ N ₃ OS ₂
258788	H	C ₁₆ H ₁₉ N ₃ OS ₂

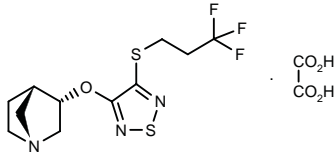
SOURCE – Lilly.

REFERENCES

1. Simon, R.L. and Whitesitt, C.A. (Eli Lilly & Co.) *Heterocyclic cpds.* WO 9739753.

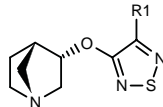
257731

endo-3-[4-(3,3,3-Trifluoropropylsulfanyl)-1,2,5-thiadiazol-3-yloxy]-1-azabicyclo[2.2.1]heptane oxalate



C11-H14-F3-N3-O-S2.C2-H2-O4; Mol wt: 415.40

ACTION – Agent for the treatment of Alzheimer’s disease, psychosis, pain, glaucoma, anxiety, mania, bipolar disorder, schizophrenia, depression, sleep disorders, epilepsy, cerebral ischemia and gastrointestinal motility disorders with affinity for muscarinic cholinergic receptors, reported to be associated with a low incidence of excessive salivation. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	Formula
258747	S(CH2)3CF3	C ₁₂ H ₁₆ F ₃ N ₃ OS ₂
258748	SCH2CH2CN	C ₁₁ H ₁₄ N ₄ OS ₂
258749	2,4-(F)2-PhCH2S	C ₁₅ H ₁₅ F ₂ N ₃ OS ₂
258750	SCH2CH2F	C ₁₀ H ₁₄ FN ₃ OS ₂
258751	SO2Bu	C ₁₂ H ₁₉ N ₃ O ₃ S ₂
258752	3-thienyl-ethynylene-CH2O	C ₁₅ H ₁₅ N ₃ O ₂ S ₂
258753	2-thienyl-ethynylene-CH2O	C ₁₅ H ₁₅ N ₃ O ₂ S ₂

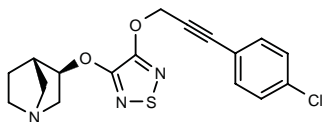
SOURCE – Lilly.

REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) *Heterocyclic cpds.* WO 9740042.

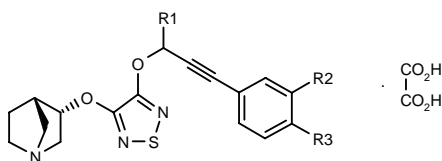
257732

(±)-*exo*-3-(1-Azabicyclo[2.2.1]hept-3-yloxy)-4-[3-(4-chlorophenyl)-2-propynyloxy]-1,2,5-thiadiazole

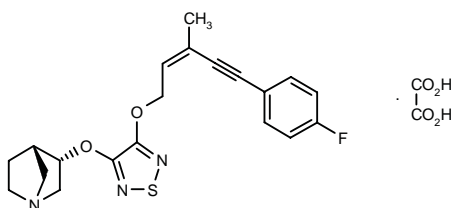


C17-H16-Cl-N3-O2-S; Mol wt: 361.85

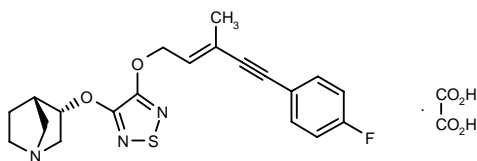
ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
258610	Me	OMe	H	C ₁₉ H ₂₁ N ₃ O ₃ S.C ₂ H ₂ O ₄
258611	H	H	Cl	C ₁₇ H ₁₆ ClN ₃ O ₂ S.C ₂ H ₂ O ₄
258612	Et	OMe	H	C ₂₀ H ₂₃ N ₃ O ₃ S.C ₂ H ₂ O ₄
258613	i-Pr	OMe	H	C ₂₁ H ₂₅ N ₃ O ₃ S.C ₂ H ₂ O ₄
258614	H	CF ₃	H	C ₁₈ H ₁₆ F ₃ N ₃ O ₂ S.C ₂ H ₂ O ₄
258649	H	H	F	C ₁₇ H ₁₆ FN ₃ O ₂ S.C ₂ H ₂ O ₄
259764	H	F	H	C ₁₇ H ₁₆ FN ₃ O ₂ S.C ₂ H ₂ O ₄



258615: C20-H20-F-N3-O2-S.C2-H2-O4



259763: C20-H20-F-N3-O2-S.C2-H2-O4

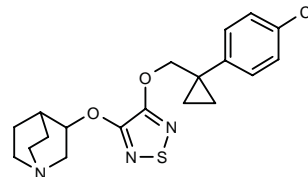
SOURCE – Lilly.

REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) *Heterocyclic cpds.* WO 9740043.

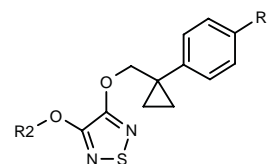
257733

(±)-3-[1-(4-Chlorophenyl)cyclopropylmethoxy]-4-(3-quinuclidinyloxy)-1,2,5-thiadiazole



C19-H22-Cl-N3-O2-S; Mol wt: 391.91

ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	Formula
258633	F	endo-(5R,6R)-1-azabicyclo[3.2.1]oct-6-yl	C ₁₉ H ₂₂ FN ₃ O ₂ S
258636	Cl	2-azabicyclo[2.2.1]hept-6-yl	C ₁₈ H ₂₀ ClN ₃ O ₂ S
258637	Cl	3(R)-Pip	C ₁₇ H ₂₀ ClN ₃ O ₂ S

SOURCE – Lilly.

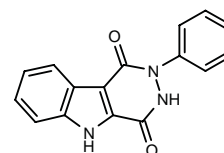
REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) *Heterocyclic cpds.* WO 9740044.

TREATMENT OF CEREBROVASCULAR DISEASES

257448

2-Phenyl-2,3,4,5-tetrahydro-1*H*-pyridazino[4,5-*b*]indole-1,4-dione



C16-H11-N3-O2; Mol wt: 277.28

ACTION – Selective and noncompetitive NMDA receptor antagonist that preferentially binds to the strychnine-insensitive glycine binding site associated with the NMDA receptor complex. Compound blocked the response to NMDA in rat cortex slices ($K_b < 150 \mu M$) and displaced [³H]-L-689560 binding to the strychnine-insensitive site in rat forebrain membranes ($IC_{50} < 50 \mu M$). Potentially useful in the treatment or prevention of neurodegenerative disorders such as stroke, cerebral ischemia, epilepsy, Huntington's chorea, Alzheimer's disease, Parkinson's disease and anoxia.

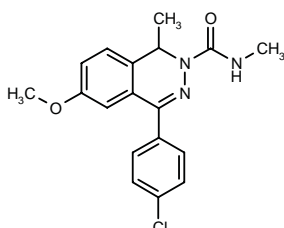
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Ladduwahetty, T. and MacLeod, A.M. (Merck Sharp & Dohme, Ltd.) *Pyridazino-indole derivs.* US 5693640.

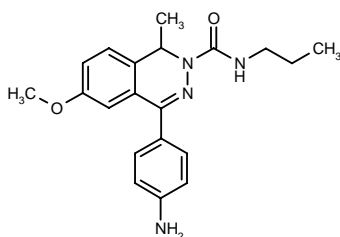
257717

4-(4-Chlorophenyl)-6-methoxy-*N*,1-dimethyl-1,2-dihydrophthalazine-2-carboxamide



C18-H18-Cl-N3-O2; Mol wt: 343.81

ACTION – A noncompetitive AMPA receptor antagonist potentially useful in the treatment of neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, hypoxia, anoxia, hypoglycemia, stroke, epilepsy, schizophrenia and migraine. Another specifically claimed compound from this series of phthalazine derivatives is:



258754: C20-H24-N4-O2

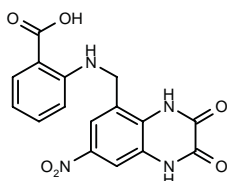
SOURCE – Schering AG.

REFERENCES

1. Ottow, E. et al. (Schering AG) *Phthalazine derivs., their preparation and their use as drugs.* DE 19617863, WO 9740020.

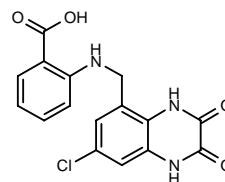
258857

2-(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl-methylamino)benzoic acid



C16-H12-N4-O6; Mol wt: 356.29

ACTION – Dual glycine-site NMDA and AMPA receptor antagonist with respective IC_{50} values in binding assays of 0.05 ± 0.02 and 0.05 ± 0.01 μ M. Potentially useful as a neuroprotective agent or for the treatment of epilepsy. Another compound from this series of 5-aryl-aminomethylquinoxaline-2,3-diones with selectivity for the glycine binding site of the NMDA receptor is:



258858: C16-H12-Cl-N3-O4

SOURCE – Novartis.

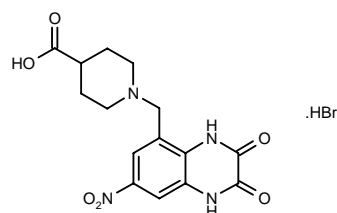
REFERENCES

1. Acklin, P. et al. (Novartis AG) *Novel 2,3-dioxo-1,2,3,4-tetrahydro-quinoxaliny derivs.* WO 9708155.

3. Auberson, Y.P. et al. *5-Aminomethylquinoxaline-2,3-diones. Part II: N-Aryl derivatives as novel NMDA/glycine and AMPA antagonists.* Bioorg Med Chem Lett 1998, 8(1): 71.

258859

1-(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl-methyl)piperidine-4-carboxylic acid hydrobromide



C15-H16-N4-O6.HBr; Mol wt: 429.23

ACTION – Potent and selective AMPA receptor antagonist, as shown in binding assays ($IC_{50} = 0.07$ μ M), with good water solubility. It exhibited significantly weaker activity at the glycine binding site of the NMDA receptor ($IC_{50} = 3.9$ μ M). Compound provided protection against electroshock-induced convulsions in mice with moderate potency ($ED_{50} = 44$ mg/kg i.p.), but ataxia was observed at doses near the ED_{50} .

SOURCE – Novartis.

REFERENCES

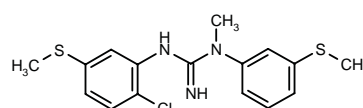
1. Acklin, P. et al. (Novartis AG) *Novel 2,3-dioxo-1,2,3,4-tetrahydro-quinoxaliny derivs.* WO 9708155.

2. Auberson, Y.P. et al. *5-Aminomethylquinoxaline-2,3-diones. Part I: A novel class of AMPA receptor antagonists.* Bioorg Med Chem Lett 1998, 8(1): 65.

CNS-5161

228550

*N*³-[2-Chloro-5-(methylsulfanyl)phenyl]-*N*¹-methyl-*N*¹-[3-(methylsulfanyl)phenyl]guanidine



C16-H18-Cl-N3-S2; Mol wt: 351.91

Hydrochloride salt, m.p. 203-4 °C.

ACTION – Potent and selective NMDA receptor ion channel blocker ($K_i = 1.87$ nM for displacement of [3 H]-MK-801 binding in rat brain membrane preparations) with much lower affinity for the σ -receptor ($K_i = 480$ nM for displacement of [3 H]-DTG binding in guinea pig brain membrane preparations). CNS-5161 is reported to be effective in a range of animal models of neuroprotection. On the basis of its pharmacological profile and safety, this compound has been selected as a clinical candidate for the prevention of neuropathic pain and neuropsychological deficits resulting from cardiac surgery.

SOURCE – Cambridge NeuroScience.

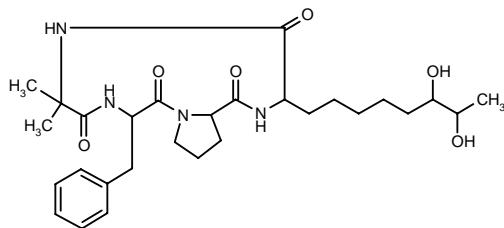
REFERENCES

1. Durant, G.J. et al. (Cambridge NeuroScience, Inc.) *Therapeutic subst. guanidines*. EP 705100, JP 96510754, WO 9427591.
2. Hu, L.-Y. et al. *Synthesis and pharmacological evaluation of n-(2,5-disubstituted phenyl)-N'-(3-substituted phenyl)-N'-methylguanidines as potent NMDA-receptor ion-channel blockers*. 25th Natl Med Chem Symp (June 18-22, Ann Arbor) 1996, Abst 85.
3. Hu, L.-Y. et al. *Synthesis and pharmacological evaluation of N-(2,5-disubstituted phenyl)-N'-(3-substituted phenyl)-N'-methylguanidines as N-methyl-D-aspartate receptor ion-channel blockers*. J Med Chem 1997, 40(26): 4281.
4. Wang, S. et al. *CNS 5161 protects against brain damage from hypoxic ischemia in neonatal rats*. Soc Neurosci Abst 1997, 23(Part 2): Abst 946.1
5. Zhou, D. et al. *Neuroprotective effect of CNS 5161, a potent NMDA ion channel antagonist, after focal ischemia in rats*. Soc Neurosci Abst 1997, 23(Part 2): Abst 946.2.
6. *Cambridge NeuroScience: Q3 1997 highlights*. Prous Science Daily Essentials December 1, 1997.
7. *Cambridge NeuroScience moves CNS-5161 to clinical trials*. Prous Science Daily Essentials September 8, 1997.
8. *CNS-5161 clinical update*. Prous Science Daily Essentials October 31, 1997.
9. *CNS-5161 shows efficacy in phase I trial*. Prous Science Daily Essentials January 9, 1998.
10. Cambridge NeuroScience Inc. Annual Report 1995.
11. Cambridge NeuroScience Second Quarter Report to Shareholders 1995, August 11.

DIHETEROPEPTIN

258360

Cyclo[2-methylalanyl- ξ -phenylalanyl- ξ -prolyl-2-(6,7-dihydroxyoctyl)glycyl]



C28-H42-N4-O6; Mol wt: 530.66

White powder, m.p. 74-6 °C, $[\alpha]_D^{25} -30.3^\circ$ (c 0.19, MeOH).

ACTION – Potential neuroprotective agent produced by the fungus *Diheterospora* sp., found to mimic the activity of transforming growth factor- β (TGF- β) using a screening system utilizing reporter gene expression. The compound induced plasminogen activator-inhibitor-1 (PAI-1) promoter gene expression in Mv1Lu cells transfected with the luciferase reporter gene at concentrations of 0.98 μ M-1 mM, comparable to TGF- β at 40 ng/ml.

TGF- β is known to both stimulate and inhibit cell growth, depending on the cell, and it is also able to protect neuronal cells from L-glutamate and β -amyloid toxicity associated with brain ischemic injury and Alzheimer's disease, respectively.

SOURCE – Univ. Tokyo, Tokyo (JP).

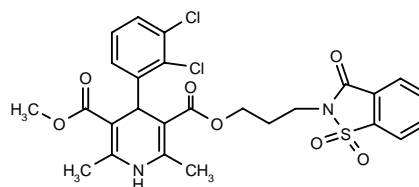
REFERENCES

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PCA-50938*

179731

4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzisothiazol-2-yl)propylmethyl diester



C26-H24-Cl2-N2-O7-S; Mol wt: 579.45

M.p. 173-7 °C.

ACTION – Neuroprotective agent, 1,4-dihydropyridine calcium antagonist with high vascular versus cardiac selectivity, as shown by inhibition of Ca^{2+} -evoked contractions in K^+ -depolarized rabbit aortic strips ($\text{IC}_{50} = 0.8$ nM), with much less potency in inhibiting contractions of electrically stimulated rabbit left atria ($\text{IC}_{50} = 521.0$ nM; selectivity index [IC_{50} atria/ IC_{50} aorta] = 686). Oral administration of title compound (20 mg/kg) to conscious spontaneously hypertensive rats produced a $35 \pm 2.6\%$ decrease in systolic blood pressure. Compound was tested for neuroprotective effect in a gerbil model of global ischemia at 0.2, 0.5 and 1 mg/kg i.p.; it produced an improvement in morbidity 2 h after the end of carotid occlusion at all doses. Animals treated with 1 mg/kg i.p. showed a significant reduction in the percent of damaged neurons in the hippocampal CA1 area 72 h after ischemia.

SOURCE – Alter.

REFERENCES

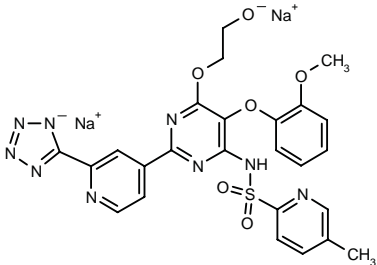
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2. Lopez, M.G. et al. *The nicotinic acetylcholine receptor of the bovine chromaffin cell, a new target for dihydropyridines*. Eur J Pharmacol Mol Pharmacol Sect 1993, 247(2): 199.
3. Sunkel, C.E. et al. *Synthesis of 3-[(2,3-dihydro-1,1,3-trioxo-1,2-benzisothiazol-2-yl)alkyl] 1,4-dihydropyridine-3,5-dicarboxylate derivatives as calcium channel modulators*. J Med Chem 1992, 35(13): 2407.
4. Zapater, P. et al. *Neuroprotection by the novel calcium antagonist PCA50938, nimodipine and flunarizine, in gerbil global brain ischemia*. Brain Res 1997, 772(1-2): 57.

*Identified compound **179731** (see **175254**) Drug Data Rep 1992, 14(3): 219.

RO-61-1790*

258492
239030 (as free acid)

N-[6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]-5-methylpyridine-2-sulfonamide disodium salt



C25-H21-N9-Na2-O6-S; Mol wt: 621.54

ACTION – Potent and selective, competitive, highly water-soluble, nonpeptide endothelin ET_A receptor antagonist, as shown in a range of binding and functional assays. *In vivo*, title compound was effective in reversing and preventing cerebral vasospasm in a canine model of subarachnoid hemorrhage. The compound was also able to inhibit the pressor effects induced by ET-1 in rats (ID₅₀ = 0.05 mg/kg i.v.) and to decrease mean arterial pressure in DOCA-salt hypertensive rats (1-10 mg/kg i.v.). Its pharmacological and pharmacokinetic profile suggests that Ro-61-1790 may be useful for preventing delayed ischemic deficits in patients with subarachnoid hemorrhage after parenteral administration.

SOURCE – Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *Novel sulfonamides*. EP 799209, WO 9619459.

2. Breu, V. *Endothelin antagonism: New data with bosentan and other compounds*. IBC Conf Endothel Inhib. Adv Ther Appl Dev (June 26-27, Philadelphia) 1997.

3. Dawson, D.A. et al. *The endothelin antagonist Ro61-1790 attenuates focal cerebral ischemic injury*. Stroke 1998, 29(1): Abst P124.

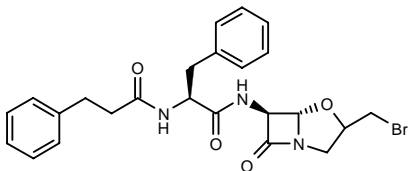
4. Roux, S. et al. *Ro 61-1790, a new hydrosoluble endothelin antagonist: General pharmacology and effects on experimental cerebral vasospasm*. J Pharmacol Exp Ther 1997, 283(3): 1110.

*Identified compound **239030** Drug Data Rep 1996, 18(10): 881.

MISCELLANEOUS NEUROLOGIC
DRUGS

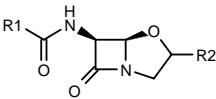
257224

(5*S*,6*S*)-3-(Bromomethyl)-6-[N-(3-phenylpropionyl)-L-phenylalanyl]amino]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one

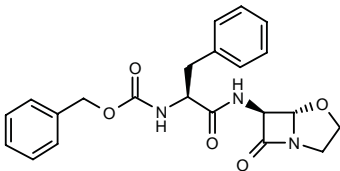


C24-H26-Br-N3-O4; Mol wt: 500.39

ACTION – Agent for the treatment of muscular dystrophy, arthritis, myocardial infarction, Alzheimer's disease, bacterial infection, the common cold, osteoporosis and cancer metastasis, an inhibitor of cysteine proteases such as cathepsin L (IC₅₀ = 0.016 μM using rat enzyme) and cathepsin B (IC₅₀ = 1.91 μM using rat enzyme). Other specifically claimed 6-substituted amino-4-oxa-1-azabicyclo[3.2.0]heptan-7-one derivatives include the following:



Compound	R1	R2	Formula
258186	PhCH2OCO-L-Phe-	H	C ₂₂ H ₂₃ N ₃ O ₅
258187	PhCH2OCO-L-Pro-	H	C ₁₈ H ₂₁ N ₃ O ₅
258188	PhCH2OCO-L-Ile-	H	C ₁₉ H ₂₅ N ₃ O ₅
258189	PhCH2OCO-L-Ala-	H	C ₁₆ H ₁₉ N ₃ O ₅
258190	PhCH2OCO-L-Leu-	H	C ₁₉ H ₂₅ N ₃ O ₅
258191	PhCH2OCO-(2-Ph)Gly-	H	C ₂₁ H ₂₁ N ₃ O ₅
258193	PhCH2CH2CO-L-Phe-	Ph	C ₂₉ H ₂₉ N ₃ O ₄



258192: C22-H23-N3-O5

SOURCES – Natl. Res. Council Canada, Ottawa, Ontario (CA); Synphar.

REFERENCES

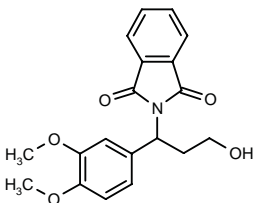
1. Singh, R. et al. (Synphar Labs., Inc.; Natl. Res. Council Canada) *6-Substd. amino-4-oxa-1-azabicyclo[3.2.0]heptan-7-one derivs. as cysteine protease inhibitors*. WO 9738008.

RESPIRATORY DRUGS

ASTHMA THERAPY

258311

N-[1-(3,4-Dimethoxyphenyl)-3-hydroxypropyl]phthalimide

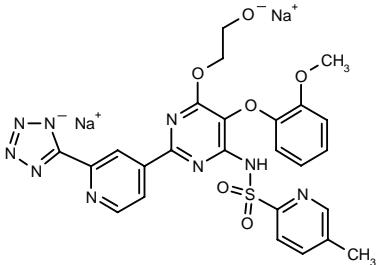


C19-H19-N-O5; Mol wt: 341.36

RO-61-1790*

258492
239030 (as free acid)

N-[6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]-5-methylpyridine-2-sulfonamide disodium salt



C25-H21-N9-Na2-O6-S; Mol wt: 621.54

ACTION – Potent and selective, competitive, highly water-soluble, nonpeptide endothelin ET_A receptor antagonist, as shown in a range of binding and functional assays. *In vivo*, title compound was effective in reversing and preventing cerebral vasospasm in a canine model of subarachnoid hemorrhage. The compound was also able to inhibit the pressor effects induced by ET-1 in rats (ID₅₀ = 0.05 mg/kg i.v.) and to decrease mean arterial pressure in DOCA-salt hypertensive rats (1-10 mg/kg i.v.). Its pharmacological and pharmacokinetic profile suggests that Ro-61-1790 may be useful for preventing delayed ischemic deficits in patients with subarachnoid hemorrhage after parenteral administration.

SOURCE – Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *Novel sulfonamides*. EP 799209, WO 9619459.

2. Breu, V. *Endothelin antagonism: New data with bosentan and other compounds*. IBC Conf Endothel Inhib. Adv Ther Appl Dev (June 26-27, Philadelphia) 1997.

3. Dawson, D.A. et al. *The endothelin antagonist Ro61-1790 attenuates focal cerebral ischemic injury*. Stroke 1998, 29(1): Abst P124.

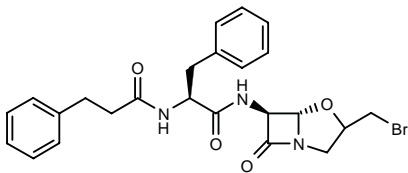
4. Roux, S. et al. *Ro 61-1790, a new hydrosoluble endothelin antagonist: General pharmacology and effects on experimental cerebral vasospasm*. J Pharmacol Exp Ther 1997, 283(3): 1110.

*Identified compound **239030** Drug Data Rep 1996, 18(10): 881.

MISCELLANEOUS NEUROLOGIC
DRUGS

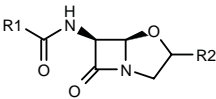
257224

(5*S*,6*S*)-3-(Bromomethyl)-6-[N-(3-phenylpropionyl)-L-phenylalanyl]amino]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one

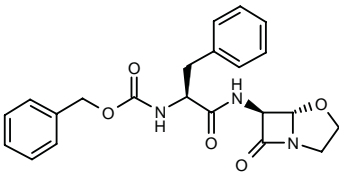


C24-H26-Br-N3-O4; Mol wt: 500.39

ACTION – Agent for the treatment of muscular dystrophy, arthritis, myocardial infarction, Alzheimer's disease, bacterial infection, the common cold, osteoporosis and cancer metastasis, an inhibitor of cysteine proteases such as cathepsin L (IC₅₀ = 0.016 μM using rat enzyme) and cathepsin B (IC₅₀ = 1.91 μM using rat enzyme). Other specifically claimed 6-substituted amino-4-oxa-1-azabicyclo[3.2.0]heptan-7-one derivatives include the following:



Compound	R1	R2	Formula
258186	PhCH2OCO-L-Phe-	H	C ₂₂ H ₂₃ N ₃ O ₅
258187	PhCH2OCO-L-Pro-	H	C ₁₈ H ₂₁ N ₃ O ₅
258188	PhCH2OCO-L-Ile-	H	C ₁₉ H ₂₅ N ₃ O ₅
258189	PhCH2OCO-L-Ala-	H	C ₁₆ H ₁₉ N ₃ O ₅
258190	PhCH2OCO-L-Leu-	H	C ₁₉ H ₂₅ N ₃ O ₅
258191	PhCH2OCO-(2-Ph)Gly-	H	C ₂₁ H ₂₁ N ₃ O ₅
258193	PhCH2CH2CO-L-Phe-	Ph	C ₂₉ H ₂₉ N ₃ O ₄



258192: C22-H23-N3-O5

SOURCES – Natl. Res. Council Canada, Ottawa, Ontario (CA); Synphar.

REFERENCES

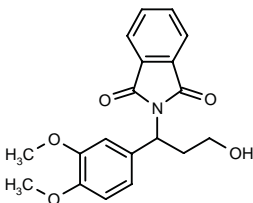
1. Singh, R. et al. (Synphar Labs., Inc.; Natl. Res. Council Canada) *6-Substd. amino-4-oxa-1-azabicyclo[3.2.0]heptan-7-one derivs. as cysteine protease inhibitors*. WO 9738008.

RESPIRATORY DRUGS

ASTHMA THERAPY

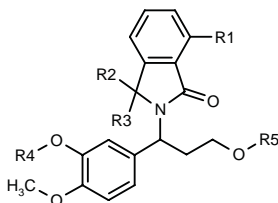
258311

N-[1-(3,4-Dimethoxyphenyl)-3-hydroxypropyl]phthalimide

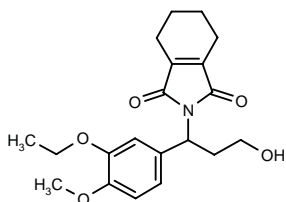


C19-H19-N-O5; Mol wt: 341.36

ACTION – Agent for the treatment of asthma, endotoxic shock, cachexia, arthritis and retrovirus replication, an inhibitor of cytokines such as tumor necrosis factor (TNF- α) and phosphodiesterases (PDE), particularly PDE III and PDE IV. Other related compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
258889	H	-O-		Et	H	C ₂₀ H ₂₁ NO ₅
258890	H	-O-		cyclopentyl	H	C ₂₃ H ₂₅ NO ₅
258891	NO ₂	-O-		Et	H	C ₂₀ H ₂₀ N ₂ O ₇
258892	NH ₂	-O-		Et	H	C ₂₀ H ₂₂ N ₂ O ₅
258894	H	H	H	Me	H	C ₁₉ H ₂₁ NO ₄
258895	H	-O-		Me	Me	C ₂₀ H ₂₁ NO ₅
258896	H	-O-		Et	Me	C ₂₁ H ₂₃ NO ₅
258897	H	-O-		cyclopentyl	Me	C ₂₄ H ₂₇ NO ₅
258898	H	-O-		Et	Et	C ₂₂ H ₂₅ NO ₅
258899	H	-O-		Et	CH ₂ Ph	C ₂₇ H ₂₇ NO ₅
258900	H	H	H	Me	Et	C ₂₁ H ₂₅ NO ₄



258893: C₂₀-H₂₅-N-O₅

SOURCE – Celgene.

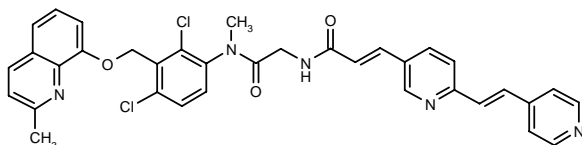
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FR-184280^{1,3}

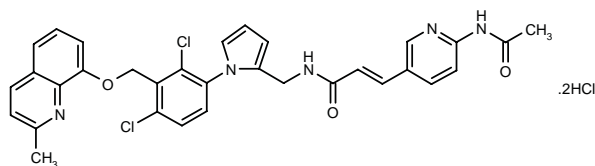
258161

N-[*N*-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-phenyl]-*N*-methylcarbamoylmethyl]-3-[6-[2(*E*)-(4-pyridyl)-vinyl]pyridin-3-yl]-2(*E*)-propenamide



C₃₅-H₂₉-Cl₂-N₅-O₃; Mol wt: 638.55

ACTION – Potent, selective and orally active, nonpeptide bradykinin B₂ receptor antagonist derived from FR-173657. *In vitro*, it inhibited B₂ receptor binding (IC₅₀ = 0.76 and 0.51 nM, respectively, in guinea pig ileum membranes and against recombinant human B₂ receptors expressed in CHO cells). It potently inhibited BK-induced bronchoconstriction in guinea pigs (91.9% inhibition at 1 mg/kg p.o.). Another compound from this series is:



FR-193517^{2,3} [258162]: C₃₂-H₂₇-Cl₂-N₅-O₃.2HCl

SOURCE – Fujisawa.

REFERENCES

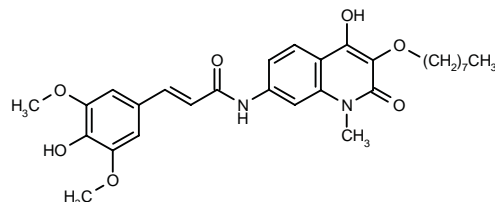
1. Oku, T. et al. (Fujisawa Pharm. Co., Ltd.) *Pyridopyrimidones, quinolines and fused N-heterocycles as bradykinin antagonists*. EP 807105, WO 9613485.

2. Oku, T. et al. (Fujisawa Pharm. Co., Ltd.) *Heterocyclic cpds. as bradykinin antagonists*. WO 9711069.

3. Abe, Y. et al. *Discovery of a new class of non-peptide bradykinin B₂ receptor antagonists with a novel framework mimicking the active conformation of the clinical candidate FR173657*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-26.

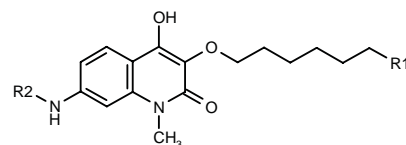
256465

4-Hydroxy-*N*-(4-hydroxy-1-methyl-3-octyloxy-2-oxo-1,2-dihydroquinolin-7-yl)-3,5-dimethoxycinnamic acid amide



C₂₉-H₃₆-N₂-O₇; Mol wt: 524.61

ACTION – Antiallergic agent proven active in a rat passive cutaneous anaphylaxis (PCA) reaction (53% inhibition at 100 mg/kg p.o.; tranilast: 54% inhibition at 200 mg/kg p.o.) and against picryl chloride-induced contact dermatitis in mice (50% inhibition at 20 mg/kg p.o.). Title compound also exhibited dose-dependent inhibition of ovalbumin-induced immediate- and delayed-type airways reactions in sensitized guinea pigs, giving 26, 31 and 43% inhibition at doses of 5, 10 and 20 mg/kg p.o., respectively. Other representative compounds within this series of quinolinone derivatives include the following:



Compound	R1	R2	Formula
258097	H	H	C ₁₆ H ₂₂ N ₂ O ₃
258098	Et	allyl	C ₂₁ H ₃₀ N ₂ O ₃

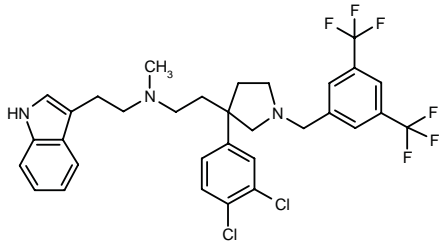
SOURCE – Dainippon Ink & Chemicals.

REFERENCES

1. Takagaki, H. et al. (Dainippon Ink & Chem., Inc.) *Quinolinone derivs. and antiallergic agents containing the same as effective ingredient*. JP 97255659.

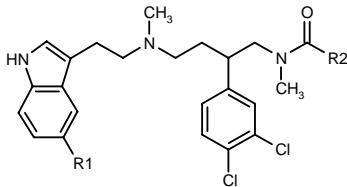
257267

N-[2-[1-[3,5-Bis(trifluoromethyl)benzyl]-3-(3,4-dichlorophenyl)pyrrolidin-3-yl]ethyl]-*N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylamine



C32-H31-Cl2-F6-N3; Mol wt: 642.51

ACTION – Antiasthmatic and antiinflammatory agent, a dual neurokinin NK₁ and NK₂ receptor antagonist, as demonstrated in binding assays by K_i values of 21 and 143 nM, respectively, against [³H]-substance P and [³H]-neurokinin A binding in CHO cells transfected with human NK₁ and NK₂ receptors. Other substituted benzene-fused hetero- and carbocyclic compounds include the following:



Compound	R1	R2	Formula
258125	H	2-Cl-6-Me-4-Pyr	C ₂₉ H ₃₁ Cl ₂ N ₄ O
258126	F	3,4,5-(MeO)3-Ph	C ₃₂ H ₃₈ Cl ₂ FN ₃ O ₄

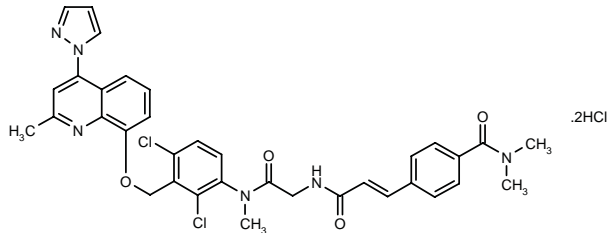
SOURCE – Schering-Plough.

REFERENCES

1. McCormick, K.D. and Lupo, A.T. Jr. (Schering Corp.) *Substd. benzene-fused hetero- and carbocyclics as neurokinin antagonists*. US 5691362.

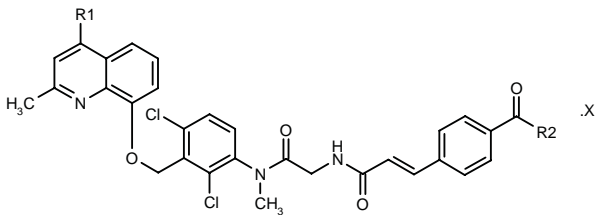
257763

*N*¹-[2,4-Dichloro-3-[4-(1-pyrazolyl)-2-methylquinolin-8-yloxymethyl]phenyl]-*N*²-[4-(*N,N*-dimethylcarbamoyl)cinnamoyl]-*N*¹-methylglycinamide dihydrochloride

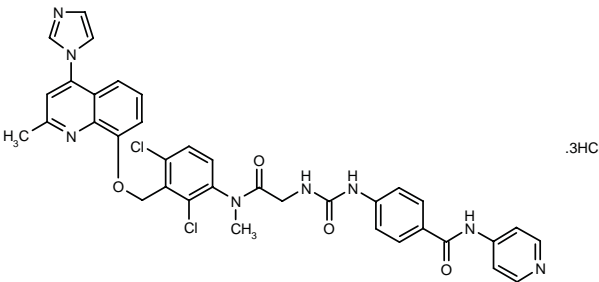


C35-H32-Cl2-N6-O4.2HCl; Mol wt: 744.50

ACTION – Agent for the treatment or prevention of asthma, allergy, inflammation, autoimmune diseases, shock and pain with bradykinin-antagonist activity (IC₅₀ = 3.3 nM against [³H]-bradykinin binding in guinea pig ileum preparations). A representative compound from a series of quinoline derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
259263	1-imidazolyl	2-Pyr-CH ₂ NH	3HCl	C ₃₉ H ₃₃ Cl ₂ N ₇ O ₄ ·3HCl
259265	1,2,4-triazol-1-yl	N(Me) ₂	HCl	C ₃₄ H ₃₁ Cl ₂ N ₇ O ₄ ·HCl
259266	1-imidazolyl	OEt		C ₃₈ H ₃₁ Cl ₂ N ₅ O ₅



259264: C36-H30-Cl2-N8-O4·3HCl

SOURCE – Fujisawa.

REFERENCES

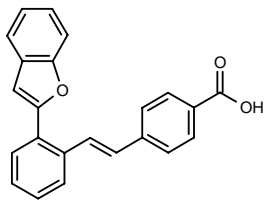
1. Oku, T. et al. (Fujisawa Pharm. Co., Ltd.) *Quinoline derivs., processes for their preparation, and their use as medicaments*. WO 9741104.

TREATMENT OF RDS AND EMPHYSEMA

NPC-18915

256905

(*E*)-4-[2-[2-(Benzofuran-2-yl)phenyl]vinyl]benzoic acid



C23-H16-O3; Mol wt: 340.38

ACTION – Potent antiinflammatory agent, a neutrophil activation inhibitor (nactin) that prevents neutrophil recruitment and subsequent tissue damage. Delayed administration of the compound was shown to ameliorate rat lung ischemia–reperfusion injury at a low dose (0.4 mg/kg) 60 min after reperfusion.

SOURCE – Scios.

REFERENCES

1. Mewshaw, R. and Hamilton, G.S. (Scios Nova, Inc.) *Anti-inflammatory benzoic acid derivs*. US 5530157.

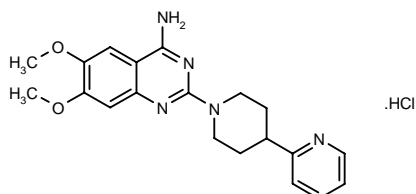
2. Yano, M. et al. *Delayed administration of NPC18915 ameliorates lung ischemia-reperfusion injury even at low dosages*. J Heart Lung Transplant 1997, 16(1): Abst 286.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

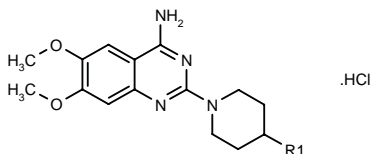
257211

6,7-Dimethoxy-2-[4-(2-pyridyl)piperidin-1-yl]quinazolin-4-amine hydrochloride



C20-H23-N5-O2.HCl; Mol wt: 401.89

ACTION – Antihypertensive agent, a potent α_{1A} - and α_{1B} -adrenoceptor and 5-HT receptor antagonist with the advantages of low neurotoxic potential, high bioavailability and a long duration of action. It inhibited [3 H]-prazosin binding to α_{1A} -adrenoceptor subtypes in rat submaxillary glands ($IC_{50} = 3.1$ nM), to α_{1B} -adrenoceptor subtypes in rat liver preparations ($IC_{50} = 8.2$ nM), and to $\alpha_{1A} + \alpha_{1C}$ -adrenoceptor subtypes in human prostate preparations ($IC_{50} = 5.0$ nM); its activity was similar to that of prazosin and 10-30 times higher than that of the α_1 -adrenoceptor antagonist WB-4101 and the 5-HT $_2$ antagonist ketanserin. Antiserotonergic activity was demonstrated by inhibition of 5-HT-induced rabbit aorta contractions ($IC_{50} = 20$ μ g/ml vs. 0.09 μ g/ml for ketanserin). Hypotensive activity was demonstrated in anesthetized normotensive rats ($ED_{30} = 0.08$ - 0.09 mg/kg i.v.), with a potency similar to that of prazosin and higher than that of verapamil and WB-4101. When tested in spontaneously hypertensive rats, compound gave an ED_{20} (0-120 min) value of 2.2 mg/kg p.o. (ED_{20} prazosin = 2.8 mg/kg p.o.), without inducing reflex tachycardia. Other representative compounds within this series of quinazolines include the following:



Compound	R1	Formula
258164	Ph	C ₂₁ H ₂₄ N ₄ O ₂ ·HCl
258165	2-thienyl	C ₁₉ H ₂₃ ClN ₄ O ₂ S·HCl
258166	2-benzofuranyl	C ₂₃ H ₂₆ ClN ₄ O ₃ ·HCl
258167	1-Naph	C ₂₆ H ₂₇ ClN ₄ O ₂ ·HCl
259518	2-MeO-Ph	C ₂₂ H ₂₇ ClN ₄ O ₃ ·HCl
259519	2-EtO-Ph	C ₂₃ H ₂₉ ClN ₄ O ₃ ·HCl
259520	2-furyl	C ₁₉ H ₂₃ ClN ₄ O ₃ ·HCl
259521	5-Me-2-furyl	C ₂₀ H ₂₆ ClN ₄ O ₃ ·HCl
259522	2-indolyl	C ₂₃ H ₂₆ ClN ₅ O ₂ ·HCl

SOURCE – Rotta.

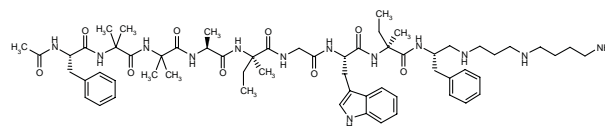
REFERENCES

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MS-681a

258345

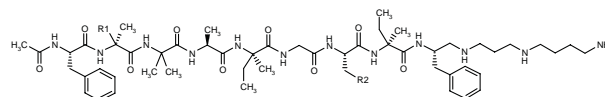
N-Acetyl-L-phenylalanyl-2-methylalanyl-2-methylalanyl-L-alanyl-D-isovalyl-glycyl-L-tryptophyl-L-isovaline 2-[3-(4-aminobutylamino)propylamino]-1(*S*)-benzylethylamide



C61-H91-N13-O9; Mol wt: 1150.47

Pale yellow solid, $[\alpha]_D^{26} +20.4^\circ$ (c 0.2, MeOH).

ACTION – Myosin light chain kinase (MLCK) inhibitor produced by the fungus *Myrothecium* sp. KY 6568. Inhibitory activity was demonstrated using purified enzyme from chicken gizzard ($IC_{50} = 0.11\text{--}0.63\ \mu\text{M}$), whereas no inhibition was observed against cAMP- and cGMP-dependent protein kinases and protein kinase C (PKC) at $100\ \mu\text{M}$. Potentially useful as a vasodilator or bronchodilator for the treatment of hypertension or asthma, or as a tool to investigate the role of MLCK in nonmuscle cells. Other compounds isolated from the same source and with a similar profile of activity are:



Compound	R1	R2	Formula
MS-681b [258346]	Me	Ph	C ₅₉ H ₉₀ N ₁₂ O ₉
MS-681c [258347]	Et	3-indolyl	C ₆₂ H ₉₃ N ₁₃ O ₉
MS-681d [258348]	Et	Ph	C ₆₀ H ₉₂ N ₁₂ O ₉

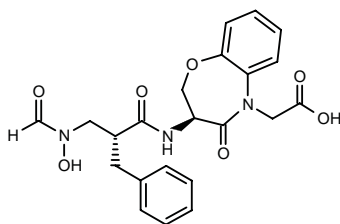
SOURCE – Kyowa Hakko.

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2. Ikuina, Y. et al. *MS-618a, b, c and d, new inhibitors of myosin light chain kinase from Myrothecium sp. II. Physico-chemical properties and structure elucidation.* J Antibiot 1997, 50(12): 998.
3. Ikuina, Y. et al. *Structures of novel inhibitors of myosin light chain kinase MS-681s.* Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1994, 36: 792.
4. Yano, H. et al. *MS-681a, b, c, and d, new inhibitors of myosin light chain kinase from Myrothecium sp. KY6568. I. Characterization of producing strain and production, isolation and biological activities.* J Antibiot 1997, 50(12): 992.

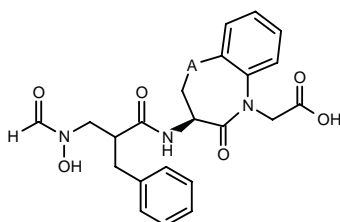
257237

2-[3(S)-[2(R)-Benzyl-3-(N-hydroxyformamido)propionamido]-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]acetic acid

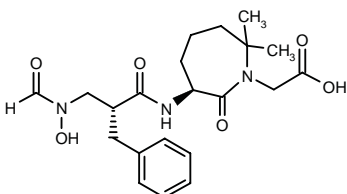


C22-H23-N3-O7; Mol wt: 441.44

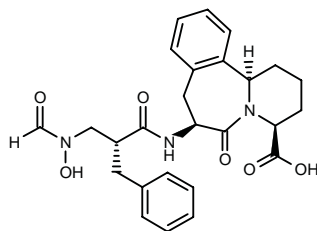
ACTION – Agent for the treatment of hypertension and congestive heart failure, an angiotensin-converting enzyme (ACE) inhibitor and/or neutral endopeptidase (NEP) inhibitor. Other specifically claimed N-formyl hydroxylamine-containing compounds include the following:



Compound	A	Isomer	Formula
258804	O	S	C ₂₂ H ₂₃ N ₃ O ₇
258806	CH ₂	R	C ₂₃ H ₂₅ N ₃ O ₆



258805: C21-H29-N3-O6



258807: C26-H29-N3-O6

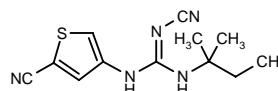
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Robl, J.A. (Bristol-Myers Squibb Co.) N-Formyl hydroxylamine containing cpds. useful as ACE inhibitors and/or NEP inhibitors. WO 9738705.

258375

2-Cyano-1-(5-cyano-3-thienyl)-3-(1,1-dimethylpropyl)-guanidine



C12-H15-N5-S; Mol wt: 261.34

Colorless plates, m.p. 162.5-5.0 °C.

ACTION – Smooth muscle relaxant ($EC_{50} = 1.2 \mu M$ in guinea pig taenia cecum preparations) with good potassium channel-opening activity, as demonstrated by the shift to the right of the dose-response curve for title compound after pretreatment with glibenclamide, a known potassium channel blocker. Compound was evaluated for its *in vivo* antihypertensive activity in anesthetized dogs, producing a decrease in blood pressure of 17.4 ± 2.4 mmHg after administration of $30 \mu g/kg$ i.v. (pinacidil: -11.3 ± 1.1 mmHg at the same dose).

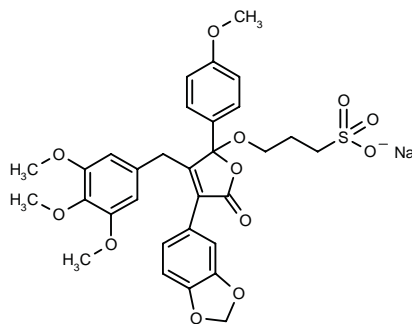
SOURCE – Kanebo.

REFERENCES

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2. Yoshiizumi, K. et al. Synthesis and structure-activity relationships of thienyl-cyanoguanidine derivatives as potassium channel openers. Chem Pharm Bull 1997, 45(12): 2005.

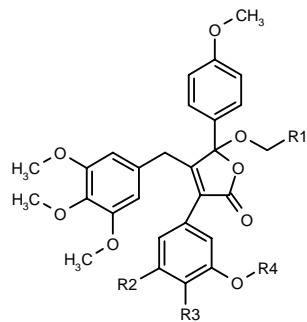
257214

3-[4-(Benzo-1,3-dioxol-5-yl)-2-(4-methoxyphenyl)-5-oxo-3-(3,4,5-trimethoxybenzyl)-2,5-dihydrofuran-2-yloxy]-propane-1-sulfonic acid sodium salt



C31-H31-Na-O12-S; Mol wt: 650.63

ACTION – Agent for the treatment of vascular diseases including atherosclerosis, restenosis, congestive heart failure, cerebral ischemia or pulmonary hypertension, an endothelin antagonist with high selectivity for human ET_A receptors ($IC_{50} = 0.15$ nM) as compared to human ET_B receptors ($IC_{50} = 1900$ nM). Compound also reduced $ET-1$ -stimulated arachidonic acid release in cultured rabbit renal artery vascular smooth muscle cells ($IC_{50} = 0.3$ nM). Other specifically claimed nonpeptide compounds with ether-linked groups include the following:



Compound	R1	R2	R3	R4	Formula
258336	4-morpholinyl-CH2	H	-OCH2-		C ₃₄ H ₃₇ NO ₁₀
258337	CH2CH2N(Me)2	H	-OCH2-		C ₃₃ H ₃₇ NO ₉
258338	CH2N(Me)2	H	-OCH2-		C ₃₂ H ₃₅ NO ₉
258339	4-morpholinyl-CH2	OMe	-OCH2-		C ₃₅ H ₃₉ NO ₁₁
258340	CH2N(Me)2	OMe	H	Me	C ₃₃ H ₃₉ NO ₉
258341	2-pyrrolidinyl	H	-OCH2-		C ₃₃ H ₃₅ NO ₉
258342	1-pyrrolidinyl-CH2	H	-OCH2-		C ₃₄ H ₃₇ NO ₉
258343	4-Me-1-Piz-CH2	H	-OCH2-		C ₃₅ H ₄₀ N ₂ O ₉

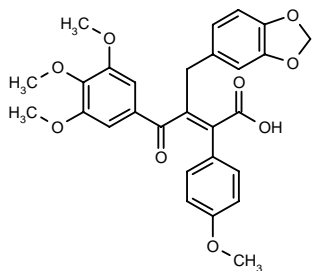
SOURCE – Warner-Lambert.

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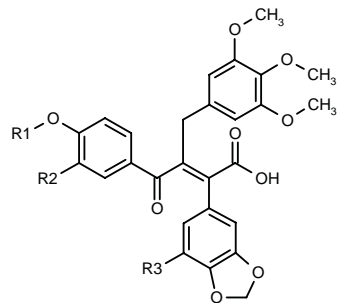
257215

3-(1,3-Benzodioxol-5-ylmethyl)-2-(4-methoxyphenyl)-4-oxo-4-(3,4,5-trimethoxyphenyl)-2(E)-butenoic acid



C28-H26-O9; Mol wt: 506.51

ACTION – Potent endothelin receptor antagonist with high selectivity for ET_A (IC₅₀ = 58 nM in Ltk- cells expressing human recombinant ET_A receptor) over ET_B receptors (IC₅₀ = 10 μM in CHO-K1 cells expressing human recombinant ET_B receptor) claimed for the treatment of a number of cardiovascular and cerebrovascular disorders, as well as cancer, asthma, diabetes, gastrointestinal disorders, benign prostatic hyperplasia, glaucoma and male erectile dysfunction. Other compounds from this series of specifically claimed ketoacids include the following:



Compound	R1	R2	R3	Formula
258575	Me	H	H	C ₂₈ H ₂₆ O ₉
258576	Et	Me	OMe	C ₃₁ H ₃₂ O ₁₀

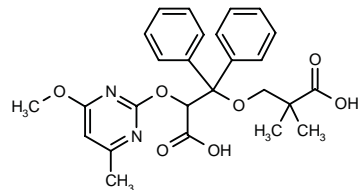
SOURCE – Warner-Lambert.

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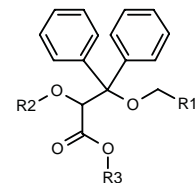
257245

3-[2-Carboxy-2-(4-methoxy-6-methylpyrimidin-2-yloxy)-1,1-diphenylethoxy]-2,2-dimethylpropionic acid



C26-H28-N2-O7; Mol wt: 480.52

ACTION – Endothelin ET_A and ET_B receptor antagonist potentially useful in the treatment of hypertension, pulmonary hypertension, acute and chronic renal failure, heart failure, cerebral ischemia, restenosis following angioplasty and prostate cancer. Other representative compounds within this series of carboxylic acid derivatives include the following:



Compound	R1	R2	R3	Formula
259758	CH2OAc	H	Me	C ₂₀ H ₂₂ O ₆
259759	CH2OAc	4-MeO-6-Me-2-pyrimidinyl	Me	C ₂₆ H ₂₈ N ₂ O ₇
259760	CH2OH	4-MeO-6-Me-2-pyrimidinyl	H	C ₂₃ H ₂₄ N ₂ O ₆
259761	C(Me)2CO2Me	H	H	C ₂₁ H ₂₄ O ₆
259762	C(Me)2CO2Me	4-MeO-6-Me-2-pyrimidinyl	H	C ₂₇ H ₃₀ N ₂ O ₇

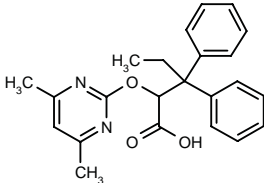
SOURCE – BASF.

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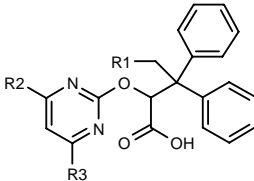
257246

2-(4,6-Dimethylpyrimidin-2-yloxy)-3,3-diphenylpentanoic acid



C23-H24-N2-O3; Mol wt: 376.45

ACTION – Antihypertensive agent also claimed for the treatment of heart failure, renal failure, cerebral ischemia and restenosis after angioplasty, an endothelin receptor antagonist with selectivity for ET_A receptors over ET_B receptors (K_i = 4 nM vs. 540 nM using human receptors expressed in CHO cells). Within this series of α-hydroxylic acid derivatives, the following are also included:



Compound	R1	R2	R3	Formula
258653	H	OMe	OMe	C ₂₂ H ₂₂ N ₂ O ₅
258654	H	OMe	Me	C ₂₂ H ₂₂ N ₂ O ₄
258655	H	Me	Me	C ₂₂ H ₂₂ N ₂ O ₃
258656	Me	OMe	OMe	C ₂₃ H ₂₄ N ₂ O ₅
258657	Me	OMe	Me	C ₂₃ H ₂₄ N ₂ O ₄
258658	OH	OMe	Me	C ₂₂ H ₂₂ N ₂ O ₅

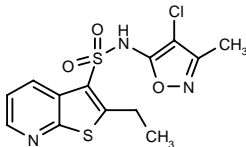
SOURCE – BASF.

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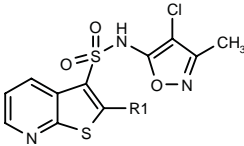
257258

N-(4-Chloro-3-methylisoxazol-5-yl)-2-ethylthieno[2,3-b]-pyridine-3-sulfonamide

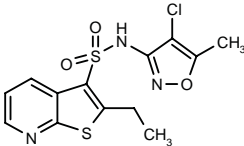


C13-H12-Cl-N3-O3-S2; Mol wt: 357.83

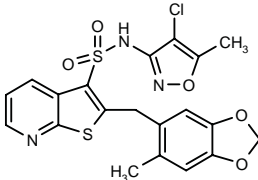
ACTION – Agent for the treatment of hypertension and other cardiovascular disorders, pulmonary hypertension, erythropoietin-mediated vasoconstriction, endotoxic shock, anaphylactic shock and hemorrhagic shock, an endothelin antagonist with higher affinity for ET_A receptors than ET_B receptors (IC₅₀ = 0.068 and 39 μM, respectively). Other compounds from this series of thienopyridine-sulfonamides include the following:



Compound	R1	Formula
258768	H	C ₁₁ H ₈ ClN ₃ O ₃ S ₂
258770	1,3-benzodioxol-5-yl-CO	C ₁₉ H ₁₂ ClN ₃ O ₆ S ₂
258771	1,3-benzodioxol-5-yl-CH2	C ₁₉ H ₁₄ ClN ₃ O ₅ S ₂
258772	2,4-(Me)2-PhCH2	C ₂₀ H ₁₈ ClN ₃ O ₃ S ₂
258774	6-Me-1,3-benzodioxol-5-yl	C ₂₀ H ₁₆ ClN ₃ O ₅ S ₂
258775	6-(CH2CH2OH)-1,3-benzodioxol-5-yl-CH2	C ₂₁ H ₁₈ ClN ₃ O ₆ S ₂
258776	1-Naph-CH2	C ₂₂ H ₁₆ ClN ₃ O ₃ S ₂
258777	2,6-(MeO)2-PhCH2	C ₂₀ H ₁₈ ClN ₃ O ₅ S ₂
258778	1,3-benzodioxol-5-yl-CH2CH2CO	C ₂₁ H ₁₆ ClN ₃ O ₆ S ₂



258767: C13-H12-Cl-N3-O3-S2



258773: C20-H16-Cl-N3-O5-S2

SOURCE – Texas Biotechnology.

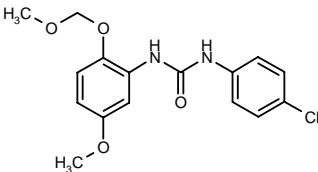
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

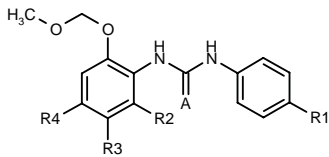
256427

N-(4-Chlorophenyl)-N'-[5-methoxy-2-(methoxymethoxy)-phenyl]urea



C16-H17-Cl-N2-O4; Mol wt: 336.77

ACTION – Antiatherosclerotic and antiischemic agent that shows potent ACAT- and lipid peroxidation-inhibitory activities. A compound within a series of phenol derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	Formula
259315	Cl	H	OMe	H	S	C ₁₆ H ₁₇ ClN ₂ O ₃ S
259316	H	H	OMe	H	S	C ₁₆ H ₁₈ N ₂ O ₃ S
259317	H	H	OC8H17	H	O	C ₂₃ H ₃₂ N ₂ O ₄
259318	H	H	OC14H29	H	O	C ₂₉ H ₄₄ N ₂ O ₄
259319	H	H	OC16H33	H	O	C ₃₁ H ₄₈ N ₂ O ₄
259320	H	OMe	OMe	OMe	O	C ₁₈ H ₂₂ N ₂ O ₆
259321	H	H	SMe	H	O	C ₁₆ H ₁₈ N ₂ O ₃ S

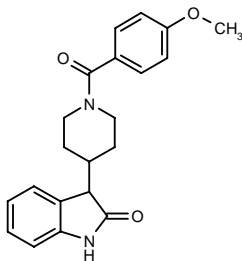
SOURCE – Tanabe Seiyaku.

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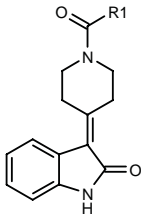
256456

3-[1-(4-Methoxybenzoyl)piperidin-4-yl]indolin-2-one

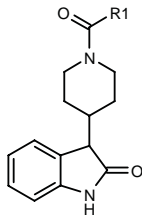


C21-H22-N2-O3; Mol wt: 350.42

ACTION – Agent for the treatment of restenosis following percutaneous transluminal coronary angioplasty (PTCA) proven to inhibit vascular intimal hypertrophy in rat thoracic aorta (49% at 30 mg/kg/day p.o.). Within this series of oxoindole derivatives, the following are also included:



Compound	R1	Formula
258225	4-(1-Pip-CH2)-Ph	C ₂₆ H ₂₉ N ₃ O ₂
258226	4-(4-Me-PhCH2O)-Ph	C ₂₆ H ₂₆ N ₂ O ₃
258227	4-MeO-PhCH=CH	C ₂₃ H ₂₂ N ₂ O ₃



Compound	R1	Formula
258228	6-EtO-3-Pyr	C ₂₁ H ₂₃ N ₃ O ₃
258229	4-MeO-PhCH2CH2	C ₂₃ H ₂₆ N ₂ O ₃

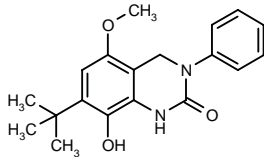
SOURCE – Taiho.

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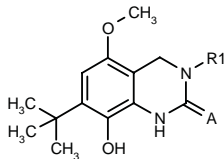
256483

7-*tert*-Butyl-8-hydroxy-5-methoxy-3-phenyl-1,2,3,4-tetrahydroquinazolin-2-one



C19-H22-N2-O3; Mol wt: 326.39

ACTION – Antiatherosclerotic and antiischemic agent with ACAT- and lipid (LDL) peroxidation-inhibitory activities and low toxicity. Within this series of phenol derivatives, the following are also included:



Compound	R1	A	Formula
258215	CH(Ph) ₂	O	C ₂₆ H ₂₈ N ₂ O ₃
258216	cyclohexyl	O	C ₁₉ H ₂₆ N ₂ O ₃
258217	Ph	S	C ₁₉ H ₂₂ N ₂ O ₂ S

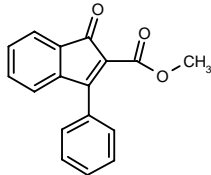
SOURCE – Tanabe Seiyaku.

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257314

1-Oxo-3-phenyl-1*H*-indene-2-carboxylic acid methyl ester



C17-H12-O3; Mol wt: 264.28

ACTION – A reversible, ATP-competitive inhibitor of fibroblast growth factor (FGF) receptor-1 tyrosine kinase ($IC_{50} = 5.1 \mu M$) with selectivity over c-Src ($IC_{50} = 25 \mu M$) and platelet-derived growth factor (PDGF) receptor tyrosine kinase (19% inhibition at $50 \mu M$). Potentially useful in the treatment of vascular proliferative disorders and certain cancers.

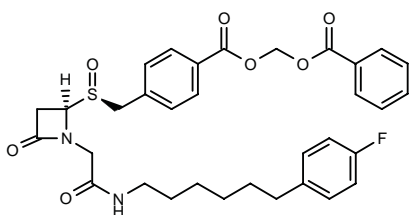
SOURCE – Warner-Lambert.

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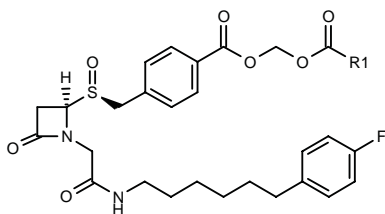
257757

(4*R*,*S*_s)-2-[4-[4-(Benzoyloxymethoxycarbonyl)benzylsulfanyl]-2-oxoazetidin-1-yl]-*N*-[6-(4-fluorophenyl)hexyl]acetamide



C33-H35-F-N2-O7-S; Mol wt: 622.71

ACTION – Antiatherosclerotic agent, an inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂; $IC_{50} = 2-4$ nM against human enzyme), expected to be useful in the treatment of atherosclerosis by virtue of its ability to inhibit the formation of lysophosphatidylcholine and oxidized free fatty acids. Also claimed for use in the treatment of diabetes, hypertension, angina pectoris and other cardiovascular disorders, as well as inflammatory disorders, Alzheimer's disease, schizophrenia and psoriasis. Within this series of specifically claimed azetidinone derivatives, the following are also included:



Compound	R1	Formula
259210	cyclohexyl	C ₃₃ H ₄₁ FN ₂ O ₇ S
259211	1-Me-cyclohexyl	C ₃₄ H ₄₃ FN ₂ O ₇ S
259212	C(Me) ₂ OMe	C ₃₁ H ₃₅ FN ₂ O ₈ S
259213	5-Me-2-oxo-1,3-dioxol-4-yl-CH ₂	C ₃₂ H ₃₅ FN ₂ O ₁₀ S

SOURCE – SmithKline Beecham.

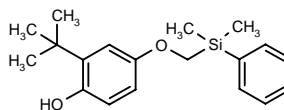
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MDL-103491

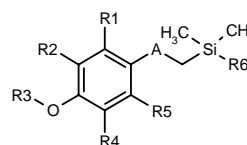
257770

2-*tert*-Butyl-4-(dimethylphenylsilylmethoxy)phenol



C19-H26-O2-Si; Mol wt: 314.50

ACTION – Antiatherosclerotic, hypolipidemic, antioxidant and antiinflammatory agent with inhibitory activity on cytokine-induced VCAM-1 and ICAM-1 expression. Other compounds from this series of specifically claimed alkyl-4-silylphenols and esters thereof include the following:



Compound	R1=R5	R2=R4	R3	R6	A	Formula
MDL-104556 [258854]	H	t-Bu	H	4-N(Me) ₂ -Ph	O	C ₂₅ H ₃₉ NO ₂ Si
MDL-104863 [258855]	H	t-Bu	COCH ₂ -CH ₂ CO ₂ H	Me	S	C ₂₂ H ₃₆ O ₄ SSi
MDL-103653 [258856]	Me	Me	H	Ph	O	C ₁₈ H ₂₄ O ₂ Si

SOURCE – Hoechst Marion Roussel.

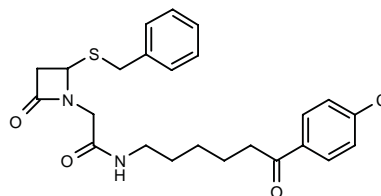
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SB-249237

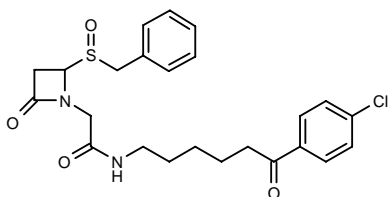
257758

2-[4-(Benzylsulfanyl)-2-oxoazetidin-1-yl]-*N*-[6-(4-chlorophenyl)-6-oxohexyl]acetamide



C24-H27-Cl-N2-O3-S; Mol wt: 459.00

ACTION – Antiatherosclerotic agent that acts by inhibiting lipoprotein-associated phospholipase A₂ (Lp-PLA₂, formerly known as PAF acetyl hydrolase), with an IC_{50} value in the nanomolar range; it is expected to be useful in the treatment of atherosclerosis by virtue of its ability to inhibit the formation of lysophosphatidylcholine and oxidized free fatty acids. Also claimed for use in the treatment of diabetes, hypertension, angina pectoris, myocardial infarction, ischemia-reperfusion injury, stroke, sepsis, rheumatoid arthritis, Alzheimer's disease, schizophrenia and psoriasis. Another specifically claimed compound from this series of monocyclic β-lactams is:



SB-249532 [258934]: C24-H27-Cl-N2-O4-S

SOURCE – SmithKline Beecham.

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ANTIARRHYTHMIC DRUGS

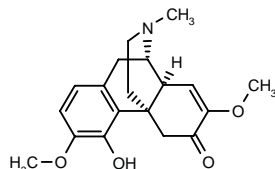
SINOMENINE

218405

(9 α , 13 α , 14 α)-4-Hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one

Cucoline

Kukoline



C19-H23-N-O4; Mol wt: 329.40

ACTION – Alkaloid isolated from the stem and root of *Sinomenium acutum* (Thumb) Rehd et Wils and the leaves of *Menispermum dauricum* DC with antiarrhythmic, analgesic, antiinflammatory, immunosuppressive and muscle relaxant activities. It is undergoing clinical evaluation for the treatment of arrhythmias and rheumatoid arthritis.

SOURCE – Xian Pharm. Factory.

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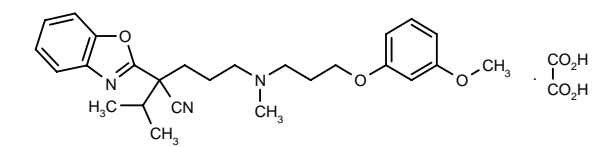
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TY-10835

257685

(±)-2-(Benzoxazol-2-yl)-2-isopropyl-5-[N-[3-(3-methoxyphenoxy)propyl]-N-methylamino]pentanenitrile oxalate



C26-H33-N3-O3.C2-H2-O4; Mol wt: 525.60

ACTION – Antiarrhythmic agent derived from verapamil that has been shown to significantly prolong cycle length of spontaneously occurring action potentials in isolated rabbit sinoatrial node with approximately the same potency as verapamil, nifedipine and diltiazem at 1 µM. Like the other compounds, it significantly decreased the rate of diastolic depolarization, the rate of rise of action potential and the amplitude of the action potential, but not the duration; similar to verapamil, it significantly decreased the maximum diastolic potential.

SOURCE – Toa Eiyo.

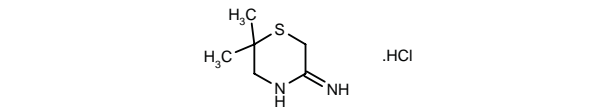
REFERENCES

1. Narita, S. et al. (Toa Eiyo Co., Ltd.) *Novel phenoxyalkylamino derivs. and their preparation*. JP 88264466.
2. Nakanishi, H. et al. *Effect of a verapamil derivative (TY-10835) on spontaneous action potentials in isolated rabbit sinoatrial node*. Pharmacometrics 1997, 54(3): 153.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

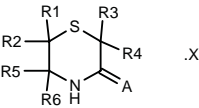
256455

6,6-Dimethylthiomorpholin-3-imine hydrochloride



C6-H12-N2-S.HCl; Mol wt: 180.70

ACTION – An inhibitor of inducible nitric oxide synthase (iNOS; IC₅₀ = 0.045 µM in mouse macrophage-derived cells) with potential in the treatment or prevention of shock, hypotension, rheumatoid arthritis, ulcerative colitis, cerebral ischemia, insulin-dependent diabetes mellitus and cancer. A representative compound from a series of thiomorpholine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	A	X	Formula
258218	H	H	H	H	Me	Me	NH		C ₆ H ₁₂ N ₂ S
258219	Et	Et	H	H	H	H	NH		C ₈ H ₁₆ N ₂ S
258220	H	H	Et	Et	H	H	NH		C ₈ H ₁₆ N ₂ S
258221	H	H	H	H	H	Me	NH		C ₆ H ₁₀ N ₂ S
258222	Et	H	H	H	H	H	NH		C ₆ H ₁₆ N ₂ S
258223	H	H	Et	H	H	H	O		C ₆ H ₁₁ NOS
258224	H	H	Et	H	H	H	NH	HI	C ₆ H ₁₂ N ₂ .HI

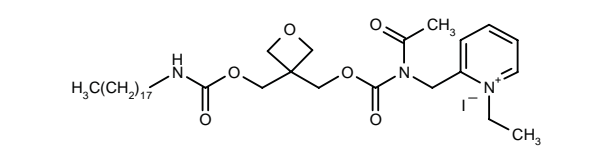
SOURCE – Ono.

REFERENCES

1. Taniguchi, N. et al. (Ono Pharm. Co., Ltd.) *Nitrogen monoxide synthase inhibitor*. JP 97249655.

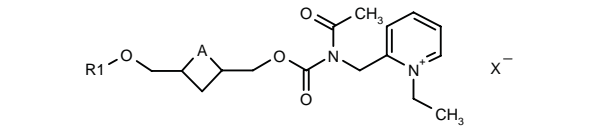
258212

2-[N-Acetyl-N-[3-(N-octadecylcarbamoxyloxymethyl)oxetan-3-ylmethoxycarbonyl]aminomethyl]-1-ethylpyridinium iodide

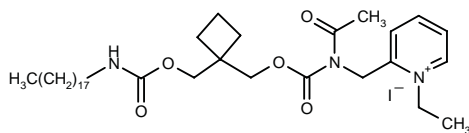
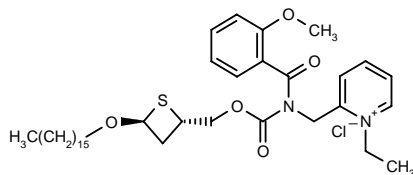
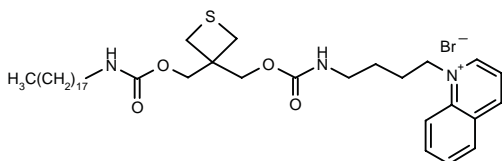


C35-H60-I-N3-O6; Mol wt: 745.78

ACTION – Potent PAF antagonist, as demonstrated in a binding assay (K_i = 22.6 nM against [³H]-C₁₈-PAF binding in rabbit platelet membranes) and by the ability to inhibit PAF-induced aggregation of rabbit platelet-rich plasma (PRP; IC₅₀ = 123 nM) and PAF-induced [¹⁴C]-serotonin release from rabbit platelets (96% inhibition at 50 nM). Potentially useful for the treatment of shock, thrombosis asthma, allergy, inflammation and gastric ulcers. A representative compound from a series of cyclic diol derivatives, wherein the following are also included:



Compound	R1	A	X	Isomer	Formula
258293	C16H33	O	I	trans	C ₃₂ H ₅₆ IN ₂ O ₅
258294	CONHC18H37	O	I	cis	C ₃₅ H ₆₀ IN ₃ O ₆
258295	CONHC18H37	O	I	trans	C ₃₅ H ₆₀ IN ₃ O ₆
258297	CONHC18H37	CH2	I	trans	C ₃₆ H ₆₂ IN ₃ O ₅
258298	CONHC18H37	S	Cl	trans	C ₃₅ H ₆₀ ClIN ₃ O ₅ S
258299	CONHC16H33	S	Cl	trans	C ₃₃ H ₅₆ ClIN ₃ O ₅ S
258302	CONHC18H37	N(COCH3)	Cl	trans	C ₃₇ H ₆₃ ClIN ₄ O ₆

**258296:** C36-H62-I-N3-O5**258300:** C37-H57-Cl-N2-O5-S**258301:** C38-H62-Br-N3-O4-S

SOURCE – Pohang Iron & Steel; Res. Inst. Ind. Sci. Technol., Kyong Sang Book-Do (KR).

REFERENCES

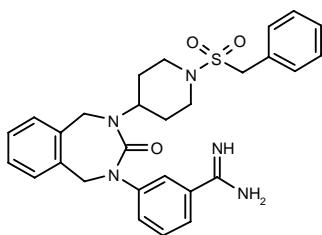
1. Woo, S.H. et al. (Pohang Iron & Steel Co., Ltd.; Res. Inst. Ind. Sci. Technol.) *Cyclic lipid derivs. as potent PAF antagonists*. US 5700817.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

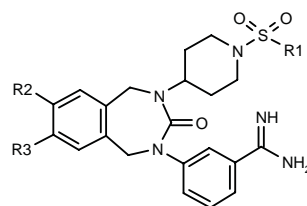
257248

2-(3-Amidinophenyl)-4-[1-(benzylsulfonyl)piperidin-4-yl]-2,3,4,5-tetrahydro-1H-2,4-benzodiazepin-3-one



C28-H31-N5-O3-S; Mol wt: 517.64

ACTION – Anticoagulant, an inhibitor of factor Xa. Also reported to inhibit serine proteases such as thrombin, plasma kallikrein and plasmin. Other representative compounds within this series of *N*-(amidinophenyl)-*N'*-(substituted)-3H-2,4-benzodiazepin-3-one derivatives include the following:



Compound	R1	R2=R3	Formula
258790	2-thienyl	H	C ₂₅ H ₂₇ N ₅ O ₃ S ₂
258791	CH ₂ Ph	OMe	C ₃₀ H ₃₅ N ₅ O ₅ S
258792	2-thienyl	OMe	C ₂₇ H ₃₁ N ₅ O ₅ S ₂

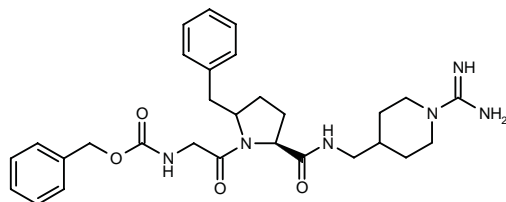
SOURCE – DuPont Merck.

REFERENCES

1. Maduskuie, T.P. Jr. et al. (The Du Pont Merck Pharm. Co.) *N*-(Amidinophenyl)-*N'*-(subst.)-3H-2,4-benzodiazepin-3-one derivs. as factor Xa inhibitors. WO 9738984.

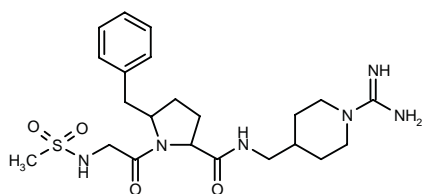
257266

N-(1-Amidinopiperidin-4-ylmethyl)-5-benzyl-1-[2-(benzyl-oxycarbonylamino)acetyl]pyrrolidine-2(*S*)-carboxamide



C29-H38-N6-O4; Mol wt: 534.66

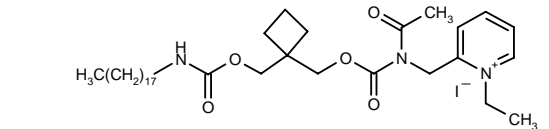
ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases, particularly thrombin. Another specifically claimed disubstituted heterocyclic compound is:

**258124:** C22-H34-N6-O4-S

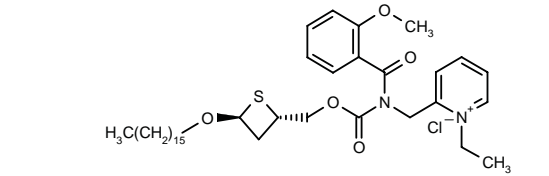
SOURCE – Bristol-Myers Squibb.

REFERENCES

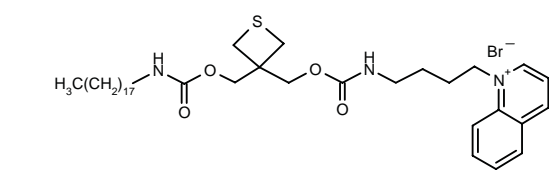
1. Das, J. et al. (Bristol-Myers Squibb Co.) *Disubstd. heterocyclic thrombin inhibitors*. US 5691356.



258296: C36-H62-I-N3-O5



258300: C37-H57-Cl-N2-O5-S



258301: C38-H62-Br-N3-O4-S

SOURCE – Pohang Iron & Steel; Res. Inst. Ind. Sci. Technol., Kyong Sang Book-Do (KR).

REFERENCES

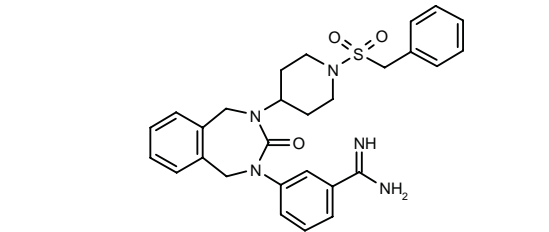
1. Woo, S.H. et al. (Pohang Iron & Steel Co., Ltd.; Res. Inst. Ind. Sci. Technol.) *Cyclic lipid derivs. as potent PAF antagonists*. US 5700817.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

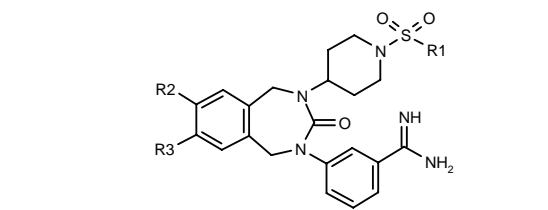
257248

2-(3-Amidinophenyl)-4-[1-(benzylsulfonyl)piperidin-4-yl]-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-3-one



C28-H31-N5-O3-S; Mol wt: 517.64

ACTION – Anticoagulant, an inhibitor of factor Xa. Also reported to inhibit serine proteases such as thrombin, plasma kallikrein and plasmin. Other representative compounds within this series of *N*-(amidinophenyl)-*N'*-(substituted)-3*H*-2,4-benzodiazepin-3-one derivatives include the following:



Compound	R1	R2=R3	Formula
258790	2-thienyl	H	C ₂₅ H ₂₇ N ₅ O ₃ S ₂
258791	CH2Ph	OMe	C ₃₀ H ₃₅ N ₅ O ₅ S
258792	2-thienyl	OMe	C ₂₇ H ₃₁ N ₅ O ₅ S ₂

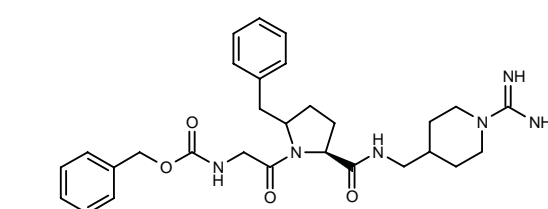
SOURCE – DuPont Merck.

REFERENCES

1. Maduskuie, T.P. Jr. et al. (The Du Pont Merck Pharm. Co.) *N*-(Amidinophenyl)-*N'*-(subst.)-3*H*-2,4-benzodiazepin-3-one derivs. as factor Xa inhibitors. WO 9738984.

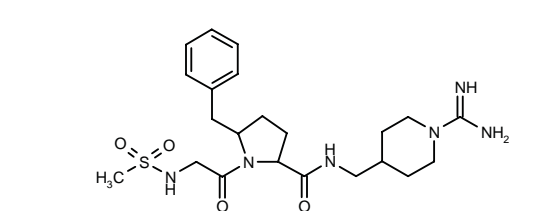
257266

N-(1-Amidinopiperidin-4-ylmethyl)-5-benzyl-1-[2-(benzyl-oxycarbonylamino)acetyl]pyrrolidine-2(*S*)-carboxamide



C29-H38-N6-O4; Mol wt: 534.66

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases, particularly thrombin. Another specifically claimed disubstituted heterocyclic compound is:



258124: C22-H34-N6-O4-S

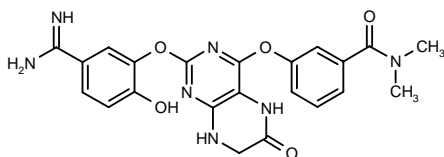
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Das, J. et al. (Bristol-Myers Squibb Co.) *Disubstd. heterocyclic thrombin inhibitors*. US 5691356.

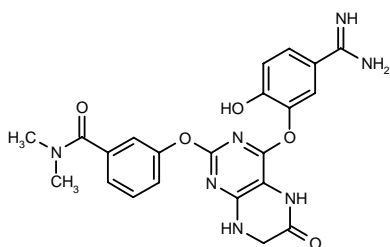
257447

3-[2-(5-Amidino-2-hydroxyphenoxy)-6-oxo-5,6,7,8-tetrahydropteridin-4-yloxy]-*N,N*-dimethylbenzamide



C22-H21-N7-O5; Mol wt: 463.45

ACTION – Anticoagulant, an inhibitor of human factor Xa. Another specifically claimed compound from this series of bicyclic pyrimidine derivatives is:



258029: C22-H21-N7-O5

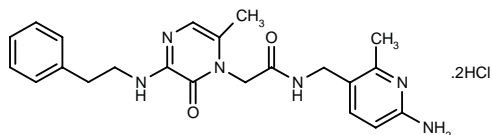
SOURCE – Berlex.

REFERENCES

1. Buckman, B.O. et al. (Berlex Labs., Inc.) *Bicyclic pyrimidine derivs. and their use as anti-coagulants*. US 5693641.

257719

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[6-methyl-2-oxo-3-(2-phenylethyl)-1,2-dihydropyrazin-1-yl]acetamide dihydrochloride



C22-H26-N6-O2.2HCl; Mol wt: 479.41

ACTION – Antithrombotic agent, a potent inhibitor of human α -thrombin with a $K_i < 1$ nM. A representative compound within a series of specifically claimed pyrazinone derivatives.

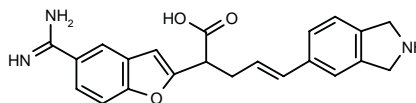
SOURCE – Merck & Co.

REFERENCES

1. Sanderson, P.E. et al. (Merck & Co., Inc.) *Pyrazinone thrombin inhibitors*. WO 9740024.

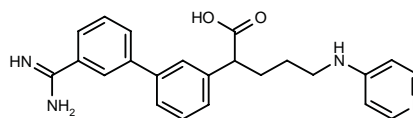
J-109063**258158**

2-(5-Amidinobenzofuran-2-yl)-5-(isoindolin-5-yl)-4(*E*)-pentenoic acid



C22-H21-N3-O3; Mol wt: 375.43

ACTION – Anticoagulant, a potent factor Xa inhibitor ($IC_{50} = 0.57$ μ M) with selectivity over thrombin (36% inhibition at 100 μ M) and improved bioavailability relative to DX-9065a. Another related compound is:



J-109047 [258159]: C23-H24-N4-O2

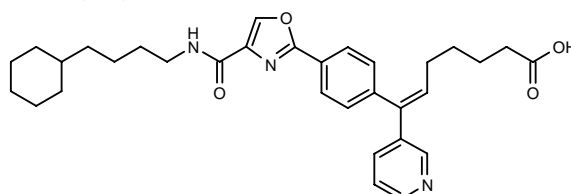
SOURCE – Banyu.

REFERENCES

1. Hayashi, K. et al. *Synthesis of factor Xa inhibitors and X-ray structure of the enzyme-substrate complex*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-30.

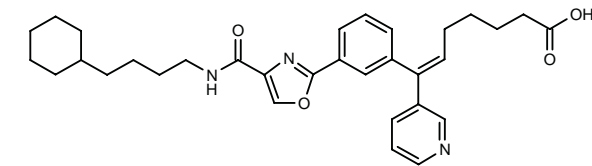
ANTIPLATELET THERAPY**258723**

7-[4-[4-[*N*-(4-Cyclohexylbutyl)carbamoyl]oxazol-2-yl]phenyl]-7-(3-pyridyl)-6(*E*)-heptenoic acid

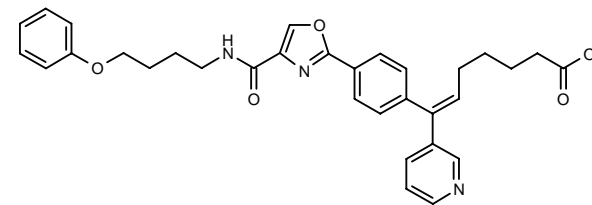


C32-H39-N3-O4; Mol wt: 529.68

ACTION – Potent dual thromboxane receptor antagonist and thromboxane synthase inhibitor, as demonstrated by IC_{50} values of 0.4 μ M and 55.0 nM, respectively, for inhibition of U-46619-induced human platelet aggregation and inhibition of TxA_2 synthase in human whole blood. In addition, it exhibited a K_d value of 9.9 nM for inhibition of [^{125}I]-IBOP binding to human platelet TxA_2 receptors. Absence of TxA_2 -agonist activity was demonstrated by the absence of a pressor response following i.v. administration of doses up to 10 mg/kg to pithed rats. It also produced > 95% inhibition of *ex vivo* TxA_2 formation in rats after oral administration of a dose of 3 mg/kg. Potentially useful for the treatment of cardiovascular and renal disorders, asthma, hepatic and intestinal damage, and for the prevention of restenosis following angioplasty or coronary bypass surgery. Other compounds from this series of specifically claimed oxazoles include the following:



259227: C32-H39-N3-O4



259228: C32-H33-N3-O5

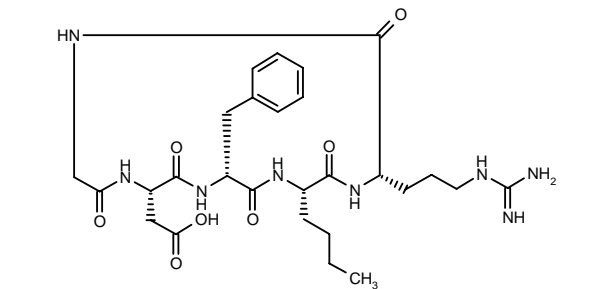
SOURCE – Lilly.

REFERENCES

1. Jakubowski, J.A. (Eli Lilly & Co.) *Carbamoyl subst. oxazoles as thromboxane receptor antagonists*. EP 811621.

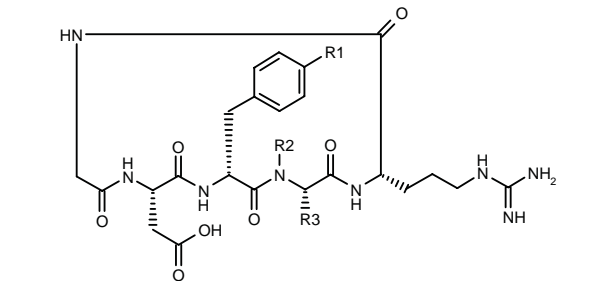
257225

Cyclo-[arginyglycyl-aspartyl-D-phenylalanyl-norleucyl]

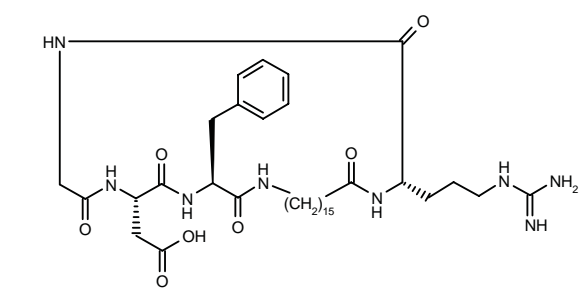


C27-H40-N8-O7; Mol wt: 588.66

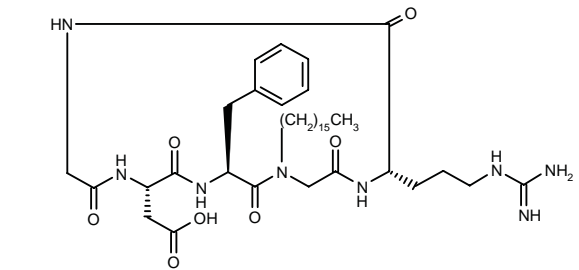
ACTION – Cell adhesion inhibitor that acts as a fibrinogen (gpIIb/IIIa) receptor antagonist and also blocks the binding of endogenous ligands to integrin receptors. Compound is reported to exhibit increased oral absorption compared to related compounds. Potentially useful in the treatment of thrombosis, myocardial infarction, arteriosclerosis, angina pectoris, stroke, inflammatory disorders, tumors, restenosis, osteoporosis and microbial infections. A representative compound from a series of cyclic peptides, wherein the following are also included:



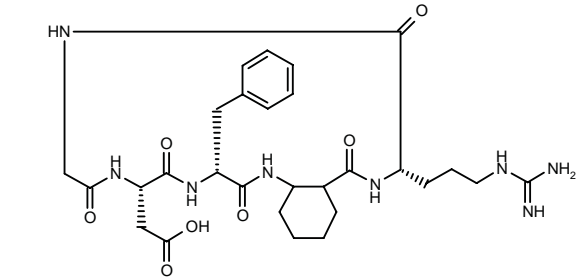
Compound	R1	R2	R3	Formula
258558	H	-(CH2)4-		C ₂₇ H ₃₈ N ₈ O ₇
258559	H	H	t-Bu	C ₂₇ H ₄₀ N ₈ O ₇
258563	Cl	H	t-Bu	C ₂₇ H ₃₉ ClN ₈ O ₇
258564	F	H	t-Bu	C ₂₇ H ₃₈ FN ₈ O ₇



258560: C37-H60-N8-O7



258561: C39-H64-N8-O7



258562: C28-H40-N8-O7

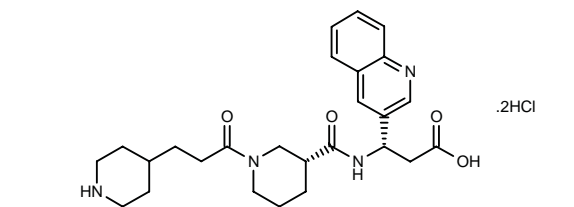
SOURCE – Merck KGaA.

REFERENCES

1. Jonczyk, A. et al. (Merck Patent GmbH) *Cyclic adhesion inhibitors*. DE 1961393, WO 9738009.

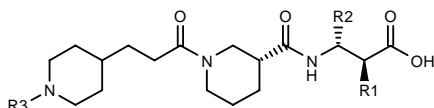
257761

3(S)-[1-[3-(4-Piperidyl)propionyl]piperidin-3(R)-ylcarbox-amido]-3-(3-quinolyl)propionic acid dihydrochloride

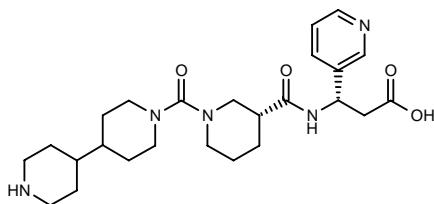


C26-H34-N4-O4.2HCl; Mol wt: 539.50

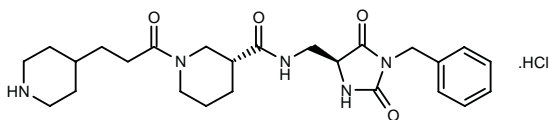
ACTION – Antithrombotic agent, a potent fibrinogen (gpIIb/IIIa) receptor antagonist ($IC_{50} = 0.2$ nM) shown to inhibit thrombin-induced aggregation of human gel-filtered platelets with an IC_{50} value of 19 nM. Compound significantly inhibited collagen- and ADP-induced platelet aggregation in an *ex vivo* model in dogs following administration of 0.1 mg/kg i.v. or 1 mg/kg p.o. In addition, it dose-dependently inhibited thrombus formation in a canine arteriovenous shunt model of thrombosis following i.v. infusion (82, 41 and 12% of thrombus weight vs. control at 3, 10 and 30 μ g/kg/min, respectively). A representative compound from a series of specifically claimed pyrrolidine, piperidine and hexahydroazepine carboxamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
259251	3-MeO-Ph-NHCONH	H	H	C ₂₅ H ₃₇ N ₅ O ₆
259252	NHCO ₂ CH ₂ Ph	H	H	C ₂₅ H ₃₆ N ₄ O ₆
259253	3-Cl-Ph-CH ₂ COCONH	H	H	C ₂₅ H ₃₅ ClN ₄ O ₆
259254	NHSO ₂ CH ₂ Ph	H	H	C ₂₄ H ₃₆ N ₄ O ₆ S
259255	3,5-(MeO) ₂ -PhNHCONH	H	H	C ₂₆ H ₃₉ N ₅ O ₇
259257	2-Naph-NHCONH	H	H	C ₂₈ H ₃₇ N ₅ O ₅
259259	NHCONHCH ₂ CH ₂ Ph	H	H	C ₂₆ H ₃₉ N ₅ O ₅
259260	H	6-Me-3-Pyr	H	C ₂₃ H ₃₄ N ₄ O ₄
259261	H	5-Br-3-Pyr	H	C ₂₂ H ₃₁ BrN ₄ O ₄
259262	H	3-Pyr	C(=NH)NH ₂	C ₂₃ H ₃₄ N ₆ O ₄



259256: C₂₅-H₃₇-N₅-O₄



259258: C₂₅-H₃₅-N₅-O₄.HCl

SOURCE – Ortho.

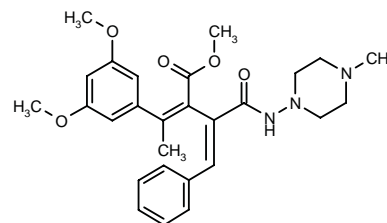
REFERENCES

1. Costanzo, M.J. et al. (Ortho Pharm. Corp.) *Carboxamide derivs. of pyrrolidine, piperidine and hexahydroazepine for the treatment of thrombosis disorders.* WO 9741102.

THROMBOLYTICS

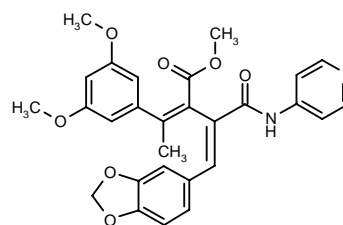
257153

3(*E*)-Benzylidene-2-[1(*Z*)-(3,5-dimethoxyphenyl)ethyl-*idene*]-*N*-(4-methylpiperazin-1-yl)succinamic acid methyl ester



C27-H33-N3-O5; Mol wt: 479.57

ACTION – Antithrombotic agent with excellent plasminogen activator inhibitor type 1 (PAI-1)-inhibitory activity, reported to possess good bioavailability and stability and low toxicity. Another compound from this series of specifically claimed butadiene derivatives is:



258105: C₂₈-H₂₆-N₂-O₇

SOURCE – Tanabe Seiyaku.

REFERENCES

1. Ohmizu, H. et al. (Tanabe Seiyaku Co., Ltd.) *Butadiene derivs. and process for preparing thereof.* WO 9736864.

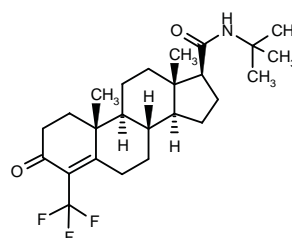
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

258685

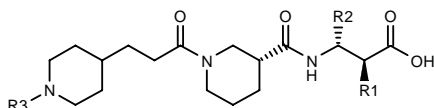
17 β -(*N*-*tert*-Butylcarbamoyl)-4-(trifluoromethyl)androst-4-en-3-one

N-*tert*-Butyl-(4-trifluoromethyl)-3-oxoandrost-4-ene-17 β -carboxamide

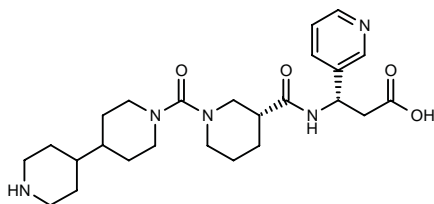


C25-H36-F3-N-O2; Mol wt: 439.56

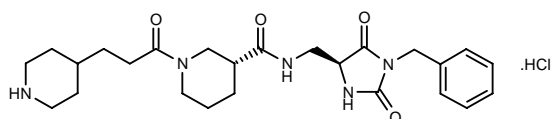
ACTION – Antithrombotic agent, a potent fibrinogen (gpIIb/IIIa) receptor antagonist ($IC_{50} = 0.2$ nM) shown to inhibit thrombin-induced aggregation of human gel-filtered platelets with an IC_{50} value of 19 nM. Compound significantly inhibited collagen- and ADP-induced platelet aggregation in an *ex vivo* model in dogs following administration of 0.1 mg/kg i.v. or 1 mg/kg p.o. In addition, it dose-dependently inhibited thrombus formation in a canine arteriovenous shunt model of thrombosis following i.v. infusion (82, 41 and 12% of thrombus weight vs. control at 3, 10 and 30 μ g/kg/min, respectively). A representative compound from a series of specifically claimed pyrrolidine, piperidine and hexahydroazepine carboxamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
259251	3-MeO-Ph-NHCONH	H	H	C ₂₅ H ₃₇ N ₅ O ₆
259252	NHCO ₂ CH ₂ Ph	H	H	C ₂₅ H ₃₆ N ₄ O ₆
259253	3-Cl-Ph-CH ₂ COCONH	H	H	C ₂₅ H ₃₅ ClN ₄ O ₆
259254	NHSO ₂ CH ₂ Ph	H	H	C ₂₄ H ₃₆ N ₄ O ₆ S
259255	3,5-(MeO) ₂ -PhNHCONH	H	H	C ₂₆ H ₃₉ N ₅ O ₇
259257	2-Naph-NHCONH	H	H	C ₂₈ H ₃₇ N ₅ O ₅
259259	NHCONHCH ₂ CH ₂ Ph	H	H	C ₂₆ H ₃₉ N ₅ O ₅
259260	H	6-Me-3-Pyr	H	C ₂₃ H ₃₄ N ₄ O ₄
259261	H	5-Br-3-Pyr	H	C ₂₂ H ₃₁ BrN ₄ O ₄
259262	H	3-Pyr	C(=NH)NH ₂	C ₂₃ H ₃₄ N ₆ O ₄



259256: C₂₅-H₃₇-N₅-O₄



259258: C₂₅-H₃₅-N₅-O₄.HCl

SOURCE – Ortho.

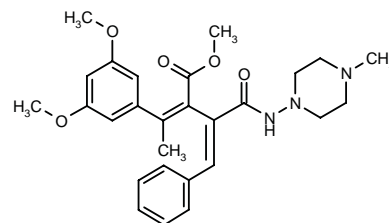
REFERENCES

1. Costanzo, M.J. et al. (Ortho Pharm. Corp.) *Carboxamide derivs. of pyrrolidine, piperidine and hexahydroazepine for the treatment of thrombosis disorders*. WO 9741102.

THROMBOLYTICS

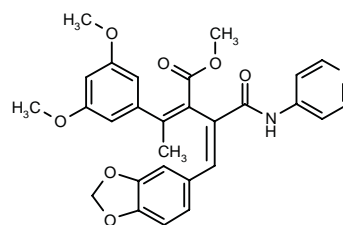
257153

3(*E*)-Benzylidene-2-[1(*Z*)-(3,5-dimethoxyphenyl)ethyl-*idene*]-*N*-(4-methylpiperazin-1-yl)succinamic acid methyl ester



C27-H33-N3-O5; Mol wt: 479.57

ACTION – Antithrombotic agent with excellent plasminogen activator inhibitor type 1 (PAI-1)-inhibitory activity, reported to possess good bioavailability and stability and low toxicity. Another compound from this series of specifically claimed butadiene derivatives is:



258105: C₂₈-H₂₆-N₂-O₇

SOURCE – Tanabe Seiyaku.

REFERENCES

1. Ohmizu, H. et al. (Tanabe Seiyaku Co., Ltd.) *Butadiene derivs. and process for preparing thereof*. WO 9736864.

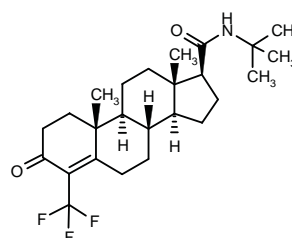
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

258685

17 β -(*N*-*tert*-Butylcarbamoyl)-4-(trifluoromethyl)androst-4-en-3-one

N-*tert*-Butyl-(4-trifluoromethyl)-3-oxoandrost-4-ene-17 β -carboxamide



C25-H36-F3-N-O2; Mol wt: 439.56

White solid, m.p. 158-9 °C.

ACTION – Potent steroid 5 α -reductase inhibitor from a novel class of 4-trifluoromethylsteroids whose activity was measured as inhibition of the conversion of [3 H]-testosterone to [3 H]-dihydrotestosterone (K_i = 20.9 nM vs. 88.2 nM for finasteride). Potentially useful in the treatment of benign prostatic hyperplasia, prostatic carcinoma, male pattern baldness, acne, alopecia and hirsutism.

SOURCE – Chinese Acad. Sci., Shanghai (CN).

REFERENCES

1. Fei, X.-S. et al. *Synthesis of 4-trifluoromethylsteroids: A novel class of steroid 5 α -reductase inhibitors.* Bioorg Med Chem Lett 1997, 7(24): 3113.

TREATMENT OF URINARY INCONTINENCE

TOLTERODINE⁺

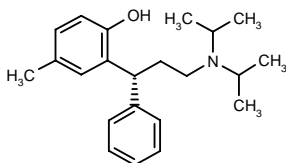
Rec INN

154881

(+)-(R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropylamine

(+)-(R)-2-[α -[2-(Diisopropylamino)ethyl]benzyl]-p-cresol

PNU-200583



C22-H31-N-O; Mol wt: 325.49

ACTION – Muscarinic receptor antagonist.

INDICATION – Treatment of unstable bladder.

PRESENTATION – Tablets, 1 and 2 mg.

PROPRIETARY NAME – *Detrusitol* (SE).

SOURCE – Pharmacia & Upjohn.

RECENT REFERENCES

1. Abrams, P. et al. *Efficacy and tolerability of tolterodine vs. oxybutynin and placebo in patients with detrusor instability.* J Urol 1997, 157(4, Suppl.): Abst 402.
2. Brynne, N. et al. *Pharmacokinetics and pharmacodynamics of tolterodine in man: A new drug for the treatment of urinary bladder overactivity.* Int J Clin Pharmacol Ther 1997, 35(7): 287.
3. Brynne, N. et al. *Inhibition of tolterodine metabolism by fluoxetine with minor change in antimuscarinic activity.* Eur J Clin Pharmacol 1997, 52(Suppl.): Abst 390.
4. Drutz, H. and Appell, R.A. *Clinical efficacy of tolterodine vs. oxybutynin and placebo in patients with unstable bladder.* Acta Obstet Gynecol Scand 1997, 76(Suppl. 167, 5): Abst FC811.4.
5. Gillberg, P.-G. and Sundquist, S. *Pharmacological profile of DD01 and desethyloxybutynin (DEOB) - the "major" metabolite of tolterodine and oxybutynin (OB), respectively.* J Urol 1997, 157(4, Suppl.): Abst 312.
6. Gozzi, P. and Pahlman, I. *Serum protein binding of tolterodine and its 5-hydroxy-methyl metabolite in different species.* 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 227.

7. Jonas, U. et al. *Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: Urodynamic evaluation.* World J Urol 1997, 15(2): 144.

8. Lindgren, A. et al. *Biotransformation of tolterodine, a novel muscarinic receptor antagonist, in mouse, rat and dog.* 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 192.

9. Nilvebrant, L. et al. *Tolterodine - A new bladder-selective antimuscarinic agent.* Eur J Pharmacol 1997, 327(2-3): 195.

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12. Palmer, L. et al. *Determination of tolterodine and the 5-hydroxymethyl metabolite in plasma, serum and urine using gas chromatography-mass spectrometry.* J Pharm Biomed Anal 1997, 16(1): 155.

13. Postlind, H. et al. *Tolterodine, a novel muscarinic receptor antagonist, is metabolized by cytochromes P450 2D6 and 3A in human liver microsomes.* 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 191.

14. Rosamilia, A. et al. *The clinical efficacy and safety of two doses of tolterodine in detrusor instability (DI).* Acta Obstet Gynecol Scand 1997, 76(Suppl. 167, 5): Abst FC811.3.

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22. *Tolterodine launch.* Pharmacia & Upjohn, Inc. Company Communication 1997, November 20.

MONOGRAPH – Graul, A. et al. *Tolterodine.* Drugs Fut 1997, 22(7): 733.

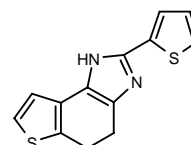
*Drug Data Rep 1992, 14(3): 225.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

258369

2-(2-Thienyl)-4,5-dihydro-1H-thieno[3,2-e]benzimidazole



C13-H10-N2-S2; Mol wt: 258.36

M.p. 271-3 °C (decomp.).

White solid, m.p. 158-9 °C.

ACTION – Potent steroid 5 α -reductase inhibitor from a novel class of 4-trifluoromethylsteroids whose activity was measured as inhibition of the conversion of [³H]-testosterone to [³H]-dihydrotestosterone (K_i = 20.9 nM vs. 88.2 nM for finasteride). Potentially useful in the treatment of benign prostatic hyperplasia, prostatic carcinoma, male pattern baldness, acne, alopecia and hirsutism.

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TREATMENT OF URINARY INCONTINENCE

TOLTERODINE⁺

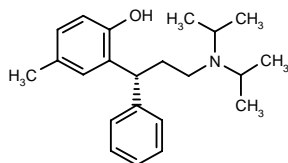
Rec INN

154881

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(+)-(R)-2-[α -[2-(Diisopropylamino)ethyl]benzyl]-p-cresol

PNU-200583



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MONOGRAPH – Graul, A. et al. *Tolterodine*. Drugs Fut 1997, 22(7): 733.

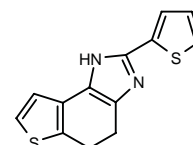
*Drug Data Rep 1992, 14(3): 225.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

258369

2-(2-Thienyl)-4,5-dihydro-1H-thieno[3,2-e]benzimidazole



C13-H10-N2-S2; Mol wt: 258.36

M.p. 271-3 °C (decomp.).

ACTION – Gastric antisecretory agent, a potent and reversible inhibitor of H^+/K^+ -ATPase activity *in vitro* ($IC_{50} = 3 \mu M$ for inhibition of K^+ -stimulated ATPase activity in canine gastric microsomes). It inhibited (50-70%) penta-gastrin-stimulated acid secretion in chronic gastric fistula rats after intraduodenal administration of 10 mg/kg. Optimization of this series is in progress due to undesirable side effects observed at higher doses.

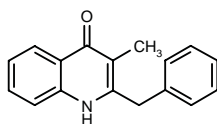
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Homma, K. et al. *Efficient synthesis and gastric (H^+/K^+)-ATPase-inhibitory activity of 2-aryl-4,5-dihydro-1H-thieno[3,2-e]benzimidazoles*. Chem Pharm Bull 1997, 45(12): 1945.

258721

2-Benzyl-3-methylquinolin-4(1H)-one



C17-H15-N-O; Mol wt: 249.31

ACTION – Quinolone with antimicrobial activity against *Helicobacter pylori*, potentially useful for the treatment and prevention of peptic ulcers, gastritis, dyspepsia and gastric cancer.

SOURCE – Pfizer.

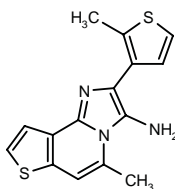
REFERENCES

1. Brown, M.F. (Pfizer, Inc.) *Antibiotic quinolones and derivs*. EP 811613.

SPI-447

257903

5-Methyl-2-(2-methylthien-3-yl)imidazo[1,2-a]thieno[3,2-c]-pyridine-3-amine



C15-H13-N3-S2; Mol wt: 299.41

ACTION – Imidazothienopyridine derivative that strongly inhibits gastric H^+/K^+ -ATPase activity in an SH group-independent manner, as shown *in vitro* using lyophilized gastric vesicles of porcine fundic mucosa ($IC_{50} = 4.2 \mu M$ at pH = 7.4; $IC_{50} = 1.05 \mu M$ at pH = 6.8).

SOURCE – Shin Nippon.

REFERENCES

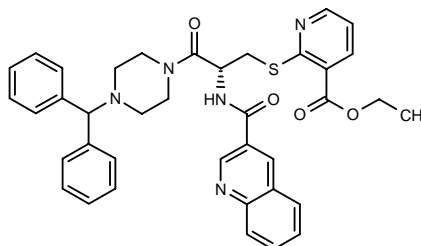
1. Tanaka, H. et al. (Shin Nippon Pharm., Inc.) *Fused imidazo[1,2-a]pyridines*. WO 9633195.

2. Ushiro, T. et al. *Inhibition of gastric H^+ , K^+ -ATPase by 3-amino-5-methyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine, SPI-447*. Jpn J Pharmacol 1997, 75(3): 303.

TREATMENT OF PANCREATIC DISORDERS

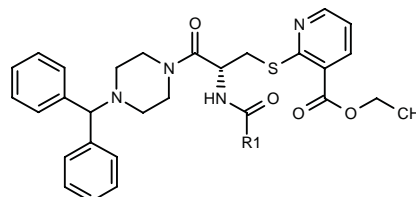
256429

2-[3-[4-(Diphenylmethyl)piperazin-1-yl]-3-oxo-2(R)-(quinolin-3-ylcarboxamido)propylsulfanyl]pyridine-3-carboxylic acid ethyl ester



C38-H37-N5-O4-S; Mol wt: 659.80

ACTION – Agent for the treatment of pancreatitis, gastric and duodenal ulcers, colitis and pancreatic cancer, a potent and selective cholecystokinin CCK_A receptor antagonist ($IC_{50} = 10 \text{ nM}$ for inhibition of CCK -8-induced guinea pig ileum contractions). Within this series of serine derivatives, the following are also included:



Compound	R1	Formula
258089	2-NH2-4-Cl-Ph	$C_{35}H_{36}ClN_5O_4S$
258090	6-Cl-2H-benzopyran-3-yl	$C_{38}H_{37}ClN_4O_5S$
258091	1,4-benzodioxan-2-yl	$C_{37}H_{38}N_4O_6S$
258092	4,8-(OH)2-2-quinolinyl	$C_{38}H_{37}N_5O_6S$

SOURCE – Tobishi.

REFERENCES

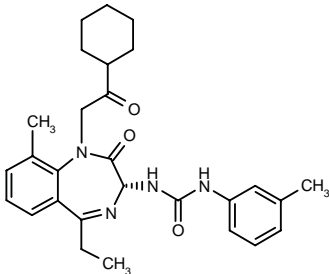
1. Ogawa, M. et al. (Tobishi Pharm. Co., Ltd.) *Anti CCK cpds. derived from serine*. JP 97227523.

FR-208419

258160

N-[1-(2-Cyclohexyl-2-oxoethyl)-5-ethyl-9-methyl-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3(*R*)-yl]-*N*'-(3-methylphenyl)urea

FR-202893 (as racemic)
FR-208418 [as (*S*)-enantiomer]



C28-H34-N4-O3; Mol wt: 474.60

ACTION – Potent, orally active dual cholecystokinin CCK_A (IC₅₀ = 0.3 nM against [¹²⁵I]-CCK-8 in rat pancreatic membranes) and CCK_B/gastrin receptor antagonist (IC₅₀ = 1.0 nM against [¹²⁵I]-CCK-8 in guinea pig cerebral cortex membranes) with well-balanced affinity for both receptors (IC₅₀ CCK_A/IC₅₀ CCK_B = 0.30). *In vivo*, it antagonized CCK-8-induced inhibition of gastric emptying in mice (ID₅₀ = 0.23 mg/kg p.o.). Antagonism of both receptor subtypes is postulated to be more effective than antagonism of either CCK_A or CCK_B receptors due to inhibitory effects on both pancreatic exocrine and gastric acid secretion. Potentially useful in the treatment of pancreatitis.

SOURCE – Fujisawa.

REFERENCES

1. Satoh, Y. et al. *Dual cholecystokinin (CCK)-A and -B receptor antagonist: Synthesis and structure-activity relationships of 9-methyl-5-alkyl-1,4-benzodiazepines*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-26.

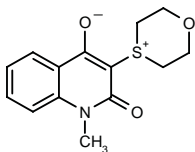
MONOGRAPH – Satoh, Y. et al. *Design of dual CCK-A and CCK-B receptor antagonists*. *Drugs Fut* 1997, 22(10): 1117.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

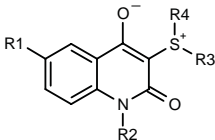
256464

1-Methyl-3-(1,4-oxathianium-4-yl)-2-oxo-1,2-dihydroquinolin-4-oxide inner salt



C14-H15-N-O3-S; Mol wt: 277.34

ACTION – Hypoglycemic agent from a series of dihydroquinoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
258099	Cl	Ph	-CH2CH2N(CH2Ph)CH2CH2-		C ₂₆ H ₂₃ ClN ₂ O ₂ S
258100	H	H	CH2CONHMe	CH2CH2OH	C ₁₄ H ₁₆ N ₂ O ₄ S
258101	H	H	4-CO2H-Ph	CH2CH2OH	C ₁₈ H ₁₅ NO ₅ S
258102	H	H	3,4,5-(MeO)3-Ph	Ph	C ₂₄ H ₂₁ NO ₅ S
258103	H	H	4-(AcNH)-Ph	4-OH-Ph	C ₂₃ H ₁₈ N ₂ O ₄ S
258104	H	Me	CH2CO2Et	CH2CH2OH	C ₁₆ H ₁₉ NO ₅ S

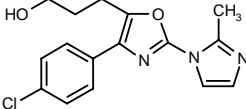
SOURCE – Otsuka.

REFERENCES

1. Shibuya and Hashimoto, K. (Otsuka Pharm. Factory, Inc.) *Dihydroquinoline derivs.* JP 97255658.

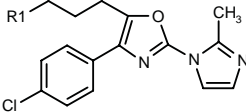
257165

3-[4-(4-Chlorophenyl)-2-(2-methylimidazol-1-yl)oxazol-5-yl]-1-propanol



C16-H16-Cl-N3-O2; Mol wt: 317.77

ACTION – Antidiabetic agent whose blood glucose-lowering effect is a consequence of its potent insulin secretion-promoting action. It produced a 23 and 18% decrease, respectively, in blood sugar levels at 60 and 120 min after a single oral dose of 30 mg/kg in KKA^Y mice. Its insulinotropic effect was demonstrated *in vitro* in MIN6 cells (272% increase at 10 μM). Other specifically claimed oxazole derivatives include the following:



Compound	R1	Formula
257889	CH2OH	C ₁₇ H ₁₈ ClN ₃ O ₂
257890	1-imidazolyl	C ₁₉ H ₁₈ ClN ₅ O
257891	CH2CH2OH	C ₁₈ H ₂₀ ClN ₃ O ₂
257892	1-imidazolyl-CH2	C ₂₀ H ₂₀ ClN ₅ O

SOURCE – Takeda.

REFERENCES

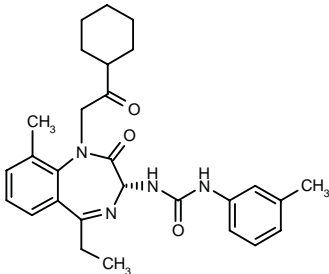
1. Momose, Y. and Odaka, H. (Takeda Chem. Ind., Ltd.) *Oxazole derivs., their production and use*. JP 97323983, WO 9736882.

FR-208419

258160

N-[1-(2-Cyclohexyl-2-oxoethyl)-5-ethyl-9-methyl-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3(*R*)-yl]-*N*'-(3-methylphenyl)urea

FR-202893 (as racemic)
FR-208418 [as (*S*)-enantiomer]



C28-H34-N4-O3; Mol wt: 474.60

ACTION – Potent, orally active dual cholecystokinin CCK_A (IC₅₀ = 0.3 nM against [¹²⁵I]-CCK-8 in rat pancreatic membranes) and CCK_B/gastrin receptor antagonist (IC₅₀ = 1.0 nM against [¹²⁵I]-CCK-8 in guinea pig cerebral cortex membranes) with well-balanced affinity for both receptors (IC₅₀ CCK_A/IC₅₀ CCK_B = 0.30). *In vivo*, it antagonized CCK-8-induced inhibition of gastric emptying in mice (ID₅₀ = 0.23 mg/kg p.o.). Antagonism of both receptor subtypes is postulated to be more effective than antagonism of either CCK_A or CCK_B receptors due to inhibitory effects on both pancreatic exocrine and gastric acid secretion. Potentially useful in the treatment of pancreatitis.

SOURCE – Fujisawa.

REFERENCES

1. Satoh, Y. et al. *Dual cholecystokinin (CCK)-A and -B receptor antagonist: Synthesis and structure-activity relationships of 9-methyl-5-alkyl-1,4-benzodiazepines*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-26.

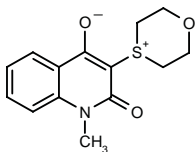
MONOGRAPH – Satoh, Y. et al. *Design of dual CCK-A and CCK-B receptor antagonists*. *Drugs Fut* 1997, 22(10): 1117.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

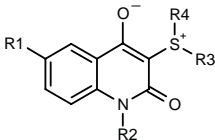
256464

1-Methyl-3-(1,4-oxathianium-4-yl)-2-oxo-1,2-dihydroquinolin-4-oxide inner salt



C14-H15-N-O3-S; Mol wt: 277.34

ACTION – Hypoglycemic agent from a series of dihydroquinoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
258099	Cl	Ph	-CH2CH2N(CH2Ph)CH2CH2-		C ₂₆ H ₂₃ ClN ₂ O ₂ S
258100	H	H	CH2CONHMe	CH2CH2OH	C ₁₄ H ₁₆ N ₂ O ₄ S
258101	H	H	4-CO2H-Ph	CH2CH2OH	C ₁₈ H ₁₅ NO ₅ S
258102	H	H	3,4,5-(MeO)3-Ph	Ph	C ₂₄ H ₂₁ NO ₅ S
258103	H	H	4-(AcNH)-Ph	4-OH-Ph	C ₂₃ H ₁₈ N ₂ O ₄ S
258104	H	Me	CH2CO2Et	CH2CH2OH	C ₁₆ H ₁₉ NO ₅ S

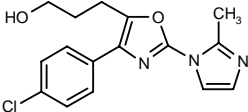
SOURCE – Otsuka.

REFERENCES

1. Shibuya and Hashimoto, K. (Otsuka Pharm. Factory, Inc.) *Dihydroquinoline derivs*. JP 97255658.

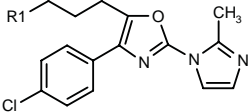
257165

3-[4-(4-Chlorophenyl)-2-(2-methylimidazol-1-yl)oxazol-5-yl]-1-propanol



C16-H16-Cl-N3-O2; Mol wt: 317.77

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257892	1-imidazolyl-CH2	C ₂₀ H ₂₀ ClN ₅ O

SOURCE – Takeda.

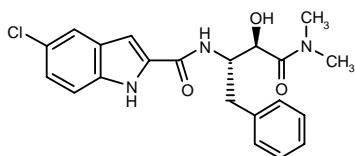
REFERENCES

1. Momose, Y. and Odaka, H. (Takeda Chem. Ind., Ltd.) *Oxazole derivs., their production and use*. JP 97323983, WO 9736882.

CP-91149***245944**

N-[1(*S*)-Benzyl-2(*R*)-(*N,N*-dimethylcarbamoyl)-2-hydroxyethyl]-5-chloro-1*H*-indole-2-carboxamide

3(*S*)-(5-Chloro-1*H*-indol-2-ylcarboxamido)-2(*R*)-hydroxy-*N,N*-dimethyl-4-phenylbutyramide



C21-H22-Cl-N3-O3; Mol wt: 399.88

ACTION – Potent, orally active human liver glycogen phosphorylase *a* inhibitor (IC_{50} = 0.13 μ M in the presence of 7.5 mM glucose); similar to caffeine, it was less potent in the absence of glucose, but its kinetics appeared to be different. The compound attenuated forskolin-stimulated glycogenolysis in human SK-Hep-1 cells (IC_{50} = 1.5 μ M) and concentration-dependently (10-100 μ M) inhibited glucagon-stimulated glycogenolysis in isolated rat hepatocytes and in primary human hepatocytes (IC_{50} = 2.1 μ M). *In vivo* in diabetic ob/ob mice, at doses of 25-50 mg/kg p.o. it produced a rapid and significant reduction in glucose levels, without producing hypoglycemia, effects at the highest dose lasting for 10 h and returning to normal by 24 h; its glucose-lowering effect was shown to be due to inhibition of glycogenolysis. The compound appears to represent the first demonstration of the potential utility of glycogenolysis inhibitors in the treatment of type II diabetes.

SOURCE – Pfizer.

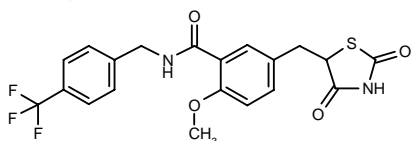
REFERENCES

- Hulin, B. et al. (Pfizer, Inc.) *Subst. N-(indole-2-carbonyl)- amides and derivs. as glycogen phosphorylase inhibitors*. WO 9639385.
- Treadway, J.L. et al. *Identification and characterization of a potent, orally-active human liver glycogen phosphorylase inhibitor with glucose-lowering activity in vivo*. IBC 2nd Int Conf Insulin Resist. Novel Drug Dev Strategies Type II Diabetes Obesity (Oct 6-7, Philadelphia) 1997.

*Identified compound **245944** Drug Data Rep 1997, 19(5): 436.

KRP-297***245873**

5-(2,4-Dioxothiazolidin-5-ylmethyl)-2-methoxy-*N*-[4-(trifluoromethyl)benzyl]benzamide



C20-H17-F3-N2-O4-S; Mol wt: 438.42

ACTION – Potent hypoglycemic agent whose insulin-sensitizing effect was evaluated in ob/ob mice, giving a 58% reduction in plasma glucose levels at a dose of 10 mg/kg/day p.o. for 5 days.

SOURCE – Kyorin.

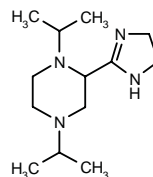
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- Maeda, T. et al. (Kyorin Pharm. Co., Ltd.) *N-Benzylthiazolidinecarboxamide derivs. and process for producing the same*. JP 97048771, WO 9638428.
- Nomura, M. et al. *Synthesis and hypoglycemic activity of novel 2,4-thiazolidinedione derivatives*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-30.

*Identified compound **245873** Drug Data Rep 1997, 19(4): 341.

S-22068**253942**

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1,4-diisopropylpiperazine



C13-H26-N4; Mol wt: 238.38

ACTION – Oral hypoglycemic agent shown to improve glucose tolerance and lower basal hyperglycemia in streptozotocin-diabetic rats after both i.p. and p.o. administration, without affecting insulin secretion or inducing hypoglycemia; it also significantly decreased the rise in basal glucose levels in fasted, glucose-challenged mice after oral administration, without affecting basal glucose or insulin levels in fed mice. The compound is suggested to act via an extrapancreatic effect, possibly increasing insulin sensitivity at peripheral tissue sites.

SOURCE – Servier.

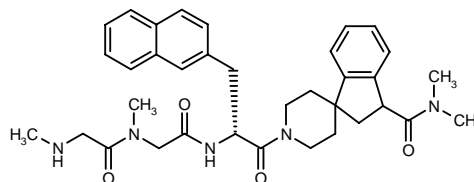
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- Godfroid, J.-J. et al. (ADIR et Cie.) *Subst. piperazines, their process of preparation and the pharmaceutical compsns. containing them*. CA 2128560, EP 638568, FR 2707984, JP 95053548, US 5492912, US 5500426.
- Pele, A. et al. *Potent antihyperglycaemic effect of an imidazoline derivative S-22068 in a rat model of type II diabetes*. Diabetologia 1997, 40(Suppl. 1): Abst 1461.
- Shih, M.-F. et al. *Effects of S-22068, an imidazoline derivative, on acute glucose tolerance and plasma insulin levels in mice*. Brit J Pharmacol 1997, 122(Suppl.): Abst 54P.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

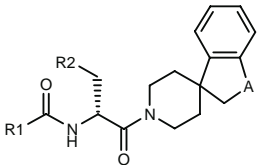
257158

N,N-Dimethyl-1'-[2(*R*)-[2-[*N*-methyl-2-(methylamino)-acetamido]acetamido]-3-(2-naphthyl)propionyl]-spiro[indane-1,4'-piperidine]-3-carboxamide

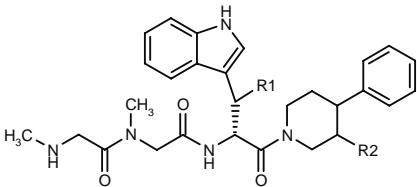


C35-H43-N5-O4; Mol wt: 597.76

ACTION – Growth hormone (GH) secretagogue able to stimulate the release of natural or endogenous GH, claimed for the treatment or prevention of various conditions, particularly osteoporosis, but also catabolic illness, immune deficiency, GH deficiency in adults or children, short stature in children, cachexia and protein loss due to chronic illness such as AIDS or cancer. Other specifically claimed piperidines, pyrrolidines and hexahydro-1*H*-azepines include the following:



Compound	R1	R2	A	Formula
258005	1-(MeNHCH2CO)- -2-pyrrolidinyl	3-indolyl	-N(SO2Me)-	C ₃₂ H ₄₀ N ₆ O ₅ S
258006	CH2N(Me)- COCH2NHMe	CH2CH2Ph	SO2	C ₂₉ H ₃₈ N ₄ O ₅ S
258007	CH2N(Me)- COCH2NH2	CH2CH2Ph	-CH(CONHPr)-	C ₃₃ H ₄₆ N ₅ O ₄
258008	CH2N(Me)- COCH2NH2	3-indolyl	-CH[CON(Me)2]-	C ₃₂ H ₄₀ N ₆ O ₄



Compound	R1	R2	Formula
258009	H	5-Me-1,3,4-oxadiazol-2-yl	C ₃₁ H ₃₇ N ₇ O ₄
258010	Me	CONHEt	C ₃₂ H ₄₂ N ₆ O ₄

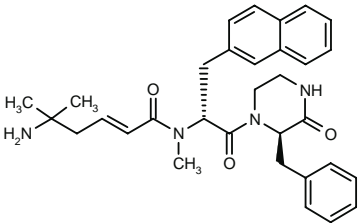
SOURCE – Merck & Co.

REFERENCES

1. Chakravarty, P.K. et al. (Merck & Co., Inc.) *Piperidines, pyrrolidines and hexahydro-1H-azepines promote release of growth hormone*. WO 9736873.

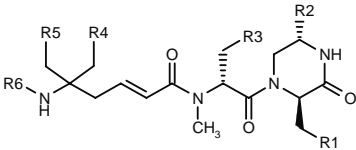
257718

5-Amino-*N*-[1(*R*)-[2(*R*)-benzyl-3-oxopiperazin-1-ylcarbonyl]-2-(2-naphthyl)ethyl]-*N*,5-dimethyl-2(*E*)-hexenamide



C32-H38-N4-O3; Mol wt: 526.68

ACTION – Agent with growth hormone (GH)-releasing properties claimed for use in the treatment of disorders caused by a deficiency in GH, e.g., in the elderly, to accelerate wound healing, in the treatment and prevention of osteoporosis, etc. Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
258628	Ph	CH2OH	2-Naph	H	H	H	C ₃₃ H ₄₀ N ₄ O ₄
258629	Ph	H	2-Naph	H	H	Me	C ₃₃ H ₄₀ N ₄ O ₃
258630	Ph	H	4-Ph-Ph	H	H	H	C ₃₄ H ₄₀ N ₄ O ₃
258631	2-thienyl	H	2-Naph	-CH2-	H	H	C ₃₁ H ₃₆ N ₄ O ₃ S
258632	2-thienyl	H	2-Naph	H	H	Me	C ₃₁ H ₃₈ N ₄ O ₃ S

SOURCE – Novo Nordisk.

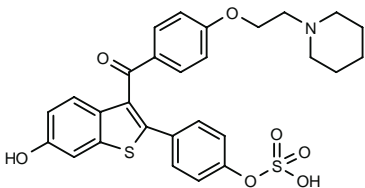
REFERENCES

1. Hansen, T.K. et al. (Novo Nordisk A/S) *Cpds. with growth hormone releasing properties*. WO 9740023.

TREATMENT OF GYNECOLOGICAL DISORDERS

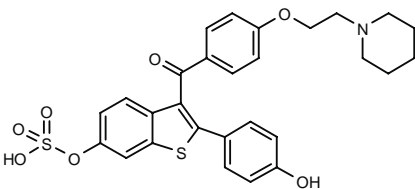
257787

Sulfuric acid 4-[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]benzothien-2-yl]phenyl monoester



C28-H27-N-O7-S2; Mol wt: 553.64

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disease, hyperlipidemia and estrogen-dependent cancers, particularly breast cancer, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, it reduced serum cholesterol levels (49.1% at 1 mg/kg/day p.o.), with little stimulatory effect on the uterus compared to 17α-ethinylestradiol and no stimulatory effect on eosinophil infiltration into the uterus. In addition, it is reported to dose-dependently prevent bone loss in ovariectomized rats. Another sulfuric acid ester of raloxifene is:



258834: C28-H27-N-O7-S2

SOURCE – Lilly.

REFERENCES

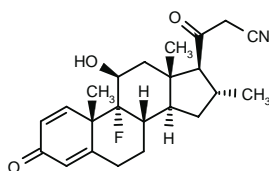
1. Clay, M.P. et al. (Eli Lilly & Co.) *Benzothiophenes, formulations containing same, and methods*. EP 806420, WO 9741851.

DERMATOLOGIC DRUGS

TOPICAL ANTIINFLAMMATORY DRUGS

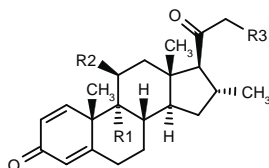
257260

9 α -Fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-diene-21-carbonitrile

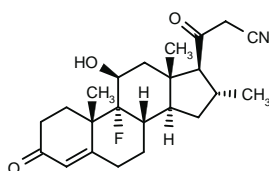


C23-H30-F-N-O3; Mol wt: 387.49

ACTION – Antiinflammatory agent and immunosuppressant with excellent local glucocorticoid activity, a representative compound from a new class of glucocorticoids that are able to inhibit the transcription of the collagenase promoter, similar to dexamethasone, but show weak or no activation of the transcription of the GRE-tk promoter, in contrast to dexamethasone. Antiinflammatory activity was demonstrated *in vivo* against croton oil-induced ear edema in mice following topical administration (ED_{50} = 2 μ g/ear vs. 1 and 4 μ g/ear, respectively, for dexamethasone and prednisolone). Immunosuppressant activity was demonstrated in the delayed-type hypersensitivity test in rats (ED_{50} = 1.5 mg/kg p.o. vs. 0.05 and 5-20 mg/kg p.o., respectively, for dexamethasone and prednisolone). Other specifically claimed compounds from this series of pregnane derivatives include the following:



Compound	R1	R2	R3	Formula
258761	F	OH	SMc	C ₂₃ H ₃₁ FO ₃ S
258762	H	OH	CH ₂ CO ₂ Me	C ₂₅ H ₃₄ O ₅
258763	H	OH	F	C ₂₂ H ₂₉ FO ₃
258766	Cl	Cl	F	C ₂₂ H ₂₇ Cl ₂ FO ₂



258760: C23-H30-F-N-O3

SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Bhatnagar, N. et al. (Roussel Uclaf) *New pregnane derivs. with no alpha-17 substituent, their medicinal use, manufacturing method and its intermediaries and related cpds*. WO 9739018.

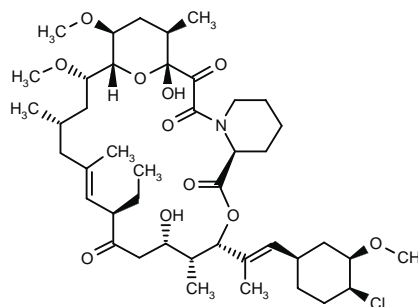
SDZ-ASM-981*

175619

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*S*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-12-[2-(4-Chloro-3-methoxycyclohexyl)-1(*E*)-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone

[3*S*(1'*R*,3'*R*,4'*S*),4*R*,5*S*,8*R*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*]-3-[2-(4-Chloro-3-methoxycyclohexyl)-1(*E*)-methylvinyl]-15,19-epoxy-8-ethyl-15,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21-tetraone

ASM-981



C43-H68-Cl-N-O11; Mol wt: 810.46

ACTION – Potent and well-tolerated antiinflammatory agent, an ascomycin macrolactam derivative for the topical and oral treatment of immunologically mediated skin diseases such as allergic contact dermatitis (ACD), psoriasis, atopic dermatitis and eczema, with a low risk for systemic immunosuppression and local side effects. In pigs with DNFB-induced ACD, topical SDZ-ASM-981 (0.1%) was as effective as clobetasol 17-propionate (0.05%), without causing skin atrophy; significant effects were observed at concentrations as low as 0.04%, whereas ciclosporin had no effect. In mice with oxazolone-induced ear edema, SDZ-ASM-981 (30 mg/kg p.o. or more) was as effective as ciclosporin at the same dose and slightly superior after s.c. administration of 1.5 mg/kg or more; it was also more potent than ciclosporin in a rat model of DNFB-induced ACD, giving significant inhibition at 12.5 mg/kg p.o. vs. 50 mg/kg p.o. for ciclosporin. It had no effect in a rat model of localized graft-versus-host reaction at 0.3 and 1 mg/kg s.c. and had little effect at 3 and 9 mg/kg s.c. Finally, in a rat model of kidney transplantation, rejection was inhibited at 15.6 mg/kg p.o. whereas ciclosporin was effective at 5.0 mg/kg p.o. SDZ-ASM-981 is currently in phase II clinical studies for the topical treatment of psoriasis, atopic dermatitis and contact dermatitis.

SOURCE – Lilly.

REFERENCES

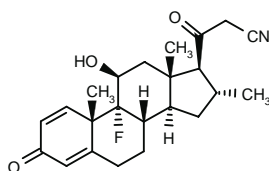
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DERMATOLOGIC DRUGS

TOPICAL ANTIINFLAMMATORY DRUGS

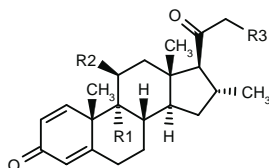
257260

9 α -Fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-diene-21-carbonitrile

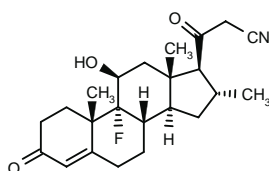


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258763	H	OH	F	C ₂₂ H ₂₉ FO ₃
258766	Cl	Cl	F	C ₂₂ H ₂₇ Cl ₂ FO ₂



258760: C23-H30-F-N-O3

SOURCE – Hoechst Marion Roussel.

REFERENCES

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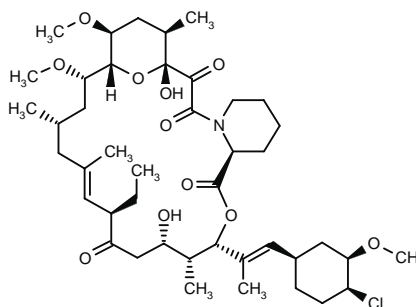
SDZ-ASM-981*

175619

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*S*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-12-[2-(4-Chloro-3-methoxycyclohexyl)-1(*E*)-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone

[3*S*(1'*R*,3'*R*,4'*S*),4*R*,5*S*,8*R*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*]-3-[2-(4-Chloro-3-methoxycyclohexyl)-1(*E*)-methylvinyl]-15,19-epoxy-8-ethyl-15,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21-tetraone

ASM-981



C43-H68-Cl-N-O11; Mol wt: 810.46

ACTION – Potent and well-tolerated antiinflammatory agent, an ascomycin macrolactam derivative for the topical and oral treatment of immunologically mediated skin diseases such as allergic contact dermatitis (ACD), psoriasis, atopic dermatitis and eczema, with a low risk for systemic immunosuppression and local side effects. In pigs with DNFB-induced ACD, topical SDZ-ASM-981 (0.1%) was as effective as clobetasol 17-propionate (0.05%), without causing skin atrophy; significant effects were observed at concentrations as low as 0.04%, whereas ciclosporin had no effect. In mice with oxazolone-induced ear edema, SDZ-ASM-981 (30 mg/kg p.o. or more) was as effective as ciclosporin at the same dose and slightly superior after s.c. administration of 1.5 mg/kg or more; it was also more potent than ciclosporin in a rat model of DNFB-induced ACD, giving significant inhibition at 12.5 mg/kg p.o. vs. 50 mg/kg p.o. for ciclosporin. It had no effect in a rat model of localized graft-versus-host reaction at 0.3 and 1 mg/kg s.c. and had little effect at 3 and 9 mg/kg s.c. Finally, in a rat model of kidney transplantation, rejection was inhibited at 15.6 mg/kg p.o. whereas ciclosporin was effective at 5.0 mg/kg p.o. SDZ-ASM-981 is currently in phase II clinical studies for the topical treatment of psoriasis, atopic dermatitis and contact dermatitis.

SOURCE – Novartis.

REFERENCES

1. Baumann, K. and Emmer, G. (Sandoz Ltd.; Sandoz Patent GmbH; Sandoz-Erfindungen VmbH) *Heteroatoms-containing tricyclic cpds.* AU 9165843, EP 427680, JP 91223291, US 5352671.

2. Cottens, S. et al. (Sandoz Ltd.; Sandoz Patent GmbH; Sandoz-Erfindungen VmbH) *Pharmaceutical compsns.* WO 9613273.

3. Guitard, P. et al. (Sandoz Ltd.; Sandoz Patent GmbH; Sandoz-Erfindungen VmbH) *Pharmaceutical compsns.* WO 9703654.

4. Jackman, M. et al. (Sandoz Ltd.; Sandoz Patent GmbH; Sandoz-Erfindungen VmbH) *Pharmaceutical compsns.* WO 9613249.

5. Baumann, K. et al. *SDZ ASM 981, a new antiinflammatory drug for use in immunologically mediated skin diseases: Activities in animal models.* Clin Dermatol 2000 (May 28-31, Vancouver) 1996, Abst 602.

6. Meingassner, J.G. et al. *Pilot studies on local and systemic side effects of SDZ ASM 981 in laboratory animals.* 12th Annu Meet Skin Pharmacol Soc (Nov 2-5, Vienna) 1995, Abst P 10.

7. Meingassner, J.G. et al. *Pharmacological profile of SDZ ASM 981, a new antiinflammatory drug for topical use in immunologically mediated skin diseases.* 12th Annu Meet Skin Pharmacol Soc (Nov 2-5, Vienna) 1995, Abst P 09.

8. Meingassner, J.G. et al. *A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin disease: In vivo pharmacology.* Brit J Dermatol 1997, 137(4): 568.

9. Meingassner, J.G. *SDZ ASM 981-a novel antiinflammatory macrolactam - does not induce skin atrophy.* Aust J Dermatol 1997, 38(Suppl. 2): Abst 5243.

10. Queille-Roussel, C. et al. *Topical treatment with the anti-inflammatory macrolactam SDZ ASM 981 inhibits established nickel contact dermatitis.* Aust J Dermatol 1997, 38(Suppl. 2): Abst 3039.

11. Reitamo, S. *Immunomodulatory drugs.* J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst C059.

12. Stütz, A. et al. *SDZ ASM 981 - A novel anti-inflammatory macrolactam.* J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst S254.

13. Van Leent, E.J.M. et al. *Topical treatment with the macrolactam SDZ ASM 981 is effective in atopic dermatitis.* Aust J Dermatol 1997, 38(Suppl. 2): Abst 4134.

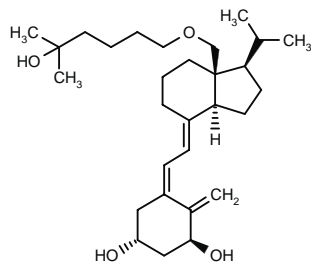
14. Sandoz Annual Report 1995.

*Identified compound **175619** (see **172636**) Drug Data Rep 1991, 13(9): 732.

ANTIPSORIATICS

257205

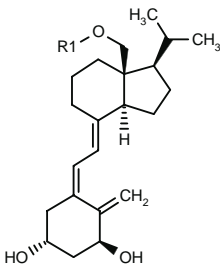
18-(5-Hydroxy-5-methylhexyloxy)-20-methyl-9,10-seco-pregna-5(Z),7(E),10(19)-triene-1(S),3(R)-diol



C29-H48-O4; Mol wt: 460.70

ACTION – Vitamin D analog with antiinflammatory, antiproliferative, differentiation-inducing and immunomodulating effects; it exhibited more potent antiproliferative and differentiation-inducing properties than 1 α ,25-dihydroxyvitamin D₃ (1 α ,25[OH]₂D₃) in U937 and HaCaT cells,

while showing a very low calciuric effect in rats (< 5% of that produced by 1 α ,25[OH]₂D₃). Potentially useful in the treatment or prevention of psoriasis, cancer, diabetes mel-litus, graft-vs.-host reaction, transplant rejection, hyper-parathyroidism, osteoporosis and neurological disorders. Other compounds from this series of specifically claimed vitamin D analogs include the following:



Compound	R1	Formula
258254	(CH2)3C(Et)2OH	C ₃₀ H ₅₀ O ₄
258255	CH2-ethynylene-C(Et)2OH	C ₃₀ H ₄₆ O ₄
258256	(CH2)3C(Me)2OH	C ₂₈ H ₄₆ O ₄
258257	CH2-ethynylene-C(Me)2OH	C ₂₈ H ₄₂ O ₄
258258	3-[C(Me)2OH]-PhCH2	C ₃₂ H ₄₆ O ₄

SOURCE – Leo.

REFERENCES

1. Grue-Sorensen, G. (Leo Pharm. Prods., Ltd. A/S) *Novel vitamin D analogues.* WO 9737972.

WOUND-HEALING AGENTS

258316

Lysyl-leucyl-valyl-glutamyl-histidyl-valyl-prolyl-gly-cyl-arginyl-prolyl-valyl-arginyl-histidyl-alanyl-gluta-minyl-cysteiny-arginine

C85-H144-N32-O21-S; Mol wt: 1982.33

ACTION – Laminin polypeptide fragment with cell adhe-sion-promoting activity, potentially useful as a wound-healing agent and as an adhesion agent for synthetic implants. Other related peptides include the following:

Arginyl-prolyl-valyl-arginyl-histidyl-alanyl-glutaminyl-cys-teiny-arginyl-valyl-cysteiny-asparyl-glycyl-asparaginy-lyl-threonyl-asparaginy-prolyl-arginyl-glutamyl-arginyl-histidine

261391: C102-H170-N44-O32-S2

Arginyl-tyrosyl-lysyl-isoleucyl-throenyl-prolyl-arginyl-argin-yl-glycyl-prolyl-prolyl-threonyl-tyrosyl-arginine

258909: C79-H129-N27-O19

Alanyl-arginyl-tyrosyl-isoleucyl-arginyl-leucyl-arginyl-leucyl-glutaminyl-arginyl-isoleucyl-arginyl-threonyl-leucine

258910: C81-H146-N30-O18

Histidyl-arginyl-aspartyl-leucyl-arginyl-aspartyl-leucyl-aspartyl-prolyl-isoleucyl-valyl-threonyl-arginyl-arginyl-tyrosyl-tyrosyl-tyrosyl-seryl-isoleucyl-lysine

258911: C116-H183-N35-O32

SOURCE – Univ. Minnesota, Minneapolis, MN (US).

REFERENCES

1. Skubitz, A.P.N. and Furcht, L.T. (Univ. Minnesota) *Laminin A chain polypeptides from the amino terminal globular domain*. US 5703205.

AMLEXANOX

Rec INN; USAN

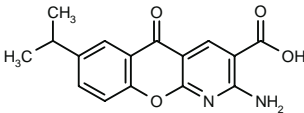
New indication

090210

2-Amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]-pyridine-3-carboxylic acid

2-Amino-7-isopropyl-1-azaxanthone-3-carboxylic acid

AA-673
Amoxanox
CHX-3673



C16-H14-N2-O4; Mol wt: 298.30

ACTION – Wound-healing agent. It was first introduced in Japan by Takeda in 1987 for the treatment of asthma and rhinitis.

INDICATION – Treatment of aphthous ulcers in patients with normal immune function.

PRESENTATION – Oral paste, 5% (50 mg amlexanox/g).

PROPRIETARY NAME – *Aphthasol* (US).

SOURCE – Block Drug.

REFERENCES

1. Khandwala, A. et al. *5% Amlexanox oral paste, a new treatment for recurrent aphthous ulcers: 1. Clinical demonstration of acceleration of healing and resolution of pain*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997, 83(2): 222.

2. Khandwala, A. et al. *5% Amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: 2. Pharmacokinetics and demonstration of clinical safety*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997, 83(2): 231.

3. *Amlexanox approvable in U.S.* Prous Science Daily Essentials May 24, 1996.

4. *Amlexanox launch*. Block Drug Co., Inc. Company Communication 1997, November 20.

5. *Clinical efficacy and safety of Aphthasol reviewed*. Prous Science Daily Essentials April 7, 1997.

6. *FDA approves first Rx treatment for oral ulcers*. FDA Press Release 1996, December 18.

7. *First Rx for oral ulcers cleared by FDA*. Prous Science Daily Essentials December 23, 1996.

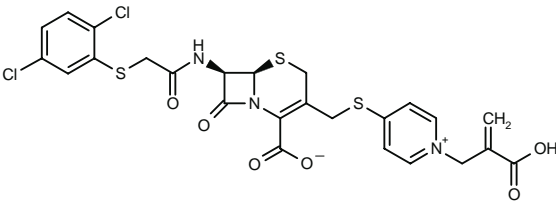
8. FDA Drug and Device Product Approvals 1996, 19(4): 4.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

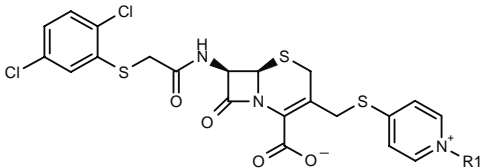
257220

(6*R*,7*R*)-3-[1-(2-Carboxy-2-propenyl)pyridinium-4-ylsulfanylmethyl]-7-[2-(2,5-dichlorophenylsulfanyl)acetamido]-3-cephem-4-carboxylate



C25-H21-Cl-N3-O6-S3; Mol wt: 591.09

ACTION – Cephalosporin antibacterial agent with potent activity against Gram-positive bacteria including methicillin-resistant strains of *Staphylococcus aureus* (MIC = 1-8 µg/ml), *Enterococcus faecalis* (MIC = 0.25-8 µg/ml) and methicillin-resistant *Staphylococcus epidermidis* (MIC = 0.015-2 µg/ml). It was active *in vivo* in mice infected with the methicillin-resistant *S. aureus* strain A27223, giving a PD₅₀ value of 0.8-22 mg/kg p.o. Within this series of specifically claimed cephalosporin derivatives, the following are also included:



Compound	R1	Formula
258179	CH2CH(OH)CO2H	C ₂₄ H ₂₁ Cl ₂ N ₃ O ₇ S ₃
258180	1-CO2H-cyclopropyl	C ₂₅ H ₂₁ Cl ₂ N ₃ O ₆ S ₃
258181	(S)-CH(CO2H)CH2CH2SO2NH2	C ₂₅ H ₂₄ Cl ₂ N ₄ O ₆ S ₄
258182	(S)-4-OH-PhCH(CO2H)	C ₂₉ H ₂₃ Cl ₂ N ₃ O ₇ S ₃
258183	CH2CH2CF2CO2H	C ₂₅ H ₂₁ Cl ₂ F ₂ N ₃ O ₆ S ₃
258184	CH2CON(Me)CH2CO2H	C ₂₆ H ₂₄ Cl ₂ N ₄ O ₇ S ₃
258185	5-tetrazolyl-S(CH2)3	C ₂₅ H ₂₃ Cl ₂ N ₇ O ₄ S ₄

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Matiskella, J.D. et al. (Bristol-Myers Squibb Co.) *Cephalosporin derivs*. WO 9737997.

Histidyl-arginyl-aspartyl-leucyl-arginyl-aspartyl-leucyl-aspartyl-prolyl-isoleucyl-valyl-threonyl-arginyl-arginyl-tyrosyl-tyrosyl-tyrosyl-seryl-isoleucyl-lysine

258911: C116-H183-N35-O32

SOURCE – Univ. Minnesota, Minneapolis, MN (US).

REFERENCES

1. Skubitz, A.P.N. and Furcht, L.T. (Univ. Minnesota) *Laminin A chain polypeptides from the amino terminal globular domain*. US 5703205.

AMLEXANOX

Rec INN; USAN

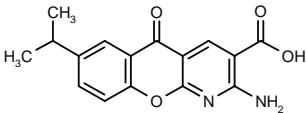
New indication

090210

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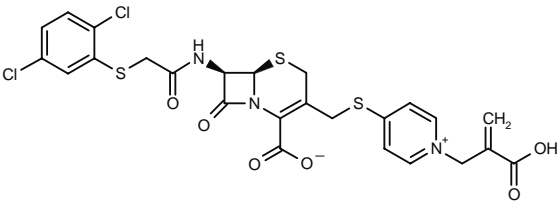
8. FDA Drug and Device Product Approvals 1996, 19(4): 4.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

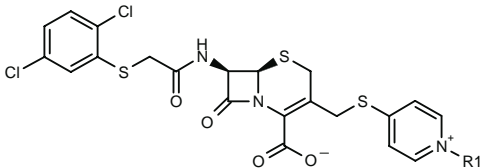
257220

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Compound	R1	Formula
258179	CH2CH(OH)CO2H	C ₂₄ H ₂₁ Cl ₂ N ₃ O ₇ S ₃
258180	1-CO2H-cyclopropyl	C ₂₅ H ₂₁ Cl ₂ N ₃ O ₆ S ₃
258181	(S)-CH(CO2H)CH2CH2SO2NH2	C ₂₅ H ₂₄ Cl ₂ N ₄ O ₆ S ₄
258182	(S)-4-OH-PhCH(CO2H)	C ₂₉ H ₂₃ Cl ₂ N ₃ O ₇ S ₃
258183	CH2CH2CF2CO2H	C ₂₅ H ₂₁ Cl ₂ F ₂ N ₃ O ₆ S ₃
258184	CH2CON(Me)CH2CO2H	C ₂₆ H ₂₄ Cl ₂ N ₄ O ₇ S ₃
258185	5-tetrazolyl-S(CH2)3	C ₂₅ H ₂₃ Cl ₂ N ₇ O ₄ S ₄

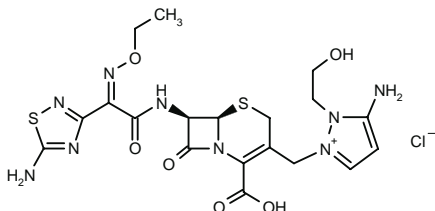
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Matiskella, J.D. et al. (Bristol-Myers Squibb Co.) *Cephalosporin derivs*. WO 9737997.

FR-86521***213079**

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(*Z*)-(ethoxyimino)acetamido]-3-[3-amino-2-(2-hydroxyethyl)pyrazolium-1-ylmethyl]-3-cephem-4-carboxylic acid chloride



C19-H24-Cl-N9-O6-S2; Mol wt: 574.03

ACTION – Cephalosporin antibacterial agent with potent, broad-spectrum activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P JC-1 (MIC = 0.39 µg/ml), methicillin-resistant *S. aureus* (MRSA) 3004 (MIC = 6.25 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC = 0.025 µg/ml or less), *Pseudomonas aeruginosa* 26 (MIC = 0.2 µg/ml) and *Klebsiella pneumoniae* 12 (MIC = 0.1 µg/ml), with activity superior to cefoselis against MRSA and *P. aeruginosa* and comparable activity against the other strains. In murine MRSA systemic infection models, it was nearly as potent as vancomycin.

SOURCE – Fujisawa.

REFERENCES

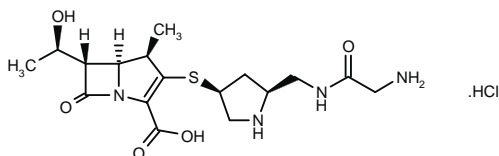
1. Takaya, T. et al. (Fujisawa Pharm. Co., Ltd.) *Cephem cpds. with antimicrobial activity*. EP 674645, JP 96504808, WO 9414818.

2. Kishi, K. et al. *Structure-activity relationships and biological properties of a novel cephalosporin FR86521 having potent activity against methicillin-resistant Staphylococcus aureus (MRSA)*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-05.

*Identified compound **213079** Drug Data Rep 1995, 17(1): 63.

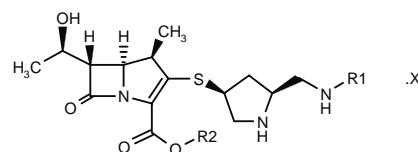
256458

(1*R*,5*S*,6*S*)-2-[5-(*S*)-(Glycylaminomethyl)pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid hydrochloride



C17-H26-N4-O5-S.HCl; Mol wt: 434.94

ACTION – Carbapenem antibacterial agent with a broad spectrum of activity and good *in vivo* stability against dehydropeptidase-I (DHP-I). It gave MICs against *Escherichia coli* NIHJ JC-2, *Haemophilus influenzae* NN400, *Pseudomonas aeruginosa* P9 and *P. aeruginosa* NC-5 of 0.05, 0.39, 0.78 and 12.5 µg/ml, respectively, vs. 0.1, 0.78, 0.78 and 25 µg/ml, respectively, for imipenem. Within this series of carbapenem compounds, the following are also included:



Compound	R1	R2	X	Formula
258241	1-Me-4-Pyr-SCH2CO	negative charge	HCl	C ₂₃ H ₃₀ N ₄ O ₅ S ₂ .HCl
258242	COCH2CH2CONH2	H		C ₁₉ H ₂₈ N ₄ O ₆ S
258243	H-L-Asn-	H	HCl	C ₁₉ H ₂₉ N ₅ O ₆ S.HCl
258244	COCONH2	H		C ₁₇ H ₂₄ N ₄ O ₆ S
258245	COCH2OH	H		C ₁₇ H ₂₅ N ₃ O ₆ S
258246	CO(CH2)3NH2	H	HCl	C ₁₉ H ₃₀ N ₄ O ₅ S.HCl
258247	H-L-Tyr-	H	HCl	C ₂₄ H ₃₂ N ₄ O ₆ S.HCl
258248	H-L-His-	H	HCl	C ₂₁ H ₃₀ N ₆ O ₅ S.HCl
258249	H-L-Gln-	H	HCl	C ₂₀ H ₃₁ N ₅ O ₆ S.HCl

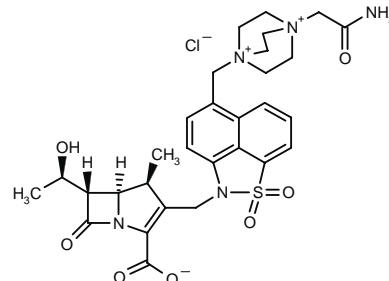
SOURCE – Takeda.

REFERENCES

1. Miwa, T. and Nagai, K. (Takeda Chem. Ind., Ltd.) *Carbapenem cpds., the preparation method thereof and pharmaceutical compsns. containing them*. JP 97249668.

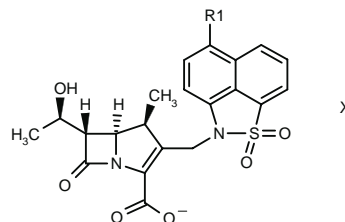
257737

(1*S*,5*R*,6*S*)-2-[5-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]octan-1-ylmethyl]-1,1-dioxo-2*H*-naphth[1,8-*cd*]isothiazol-2-ylmethyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate chloride

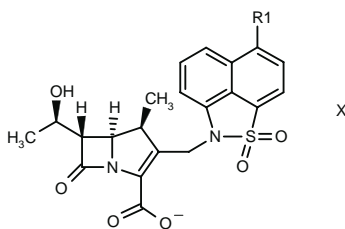


C30-H36-Cl-N5-O7-S; Mol wt: 646.16

ACTION – Carbapenem antibacterial agent with activity against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other compounds from this series of specifically claimed carbapenems substituted at the 2-position with a naphthosultam group include the following:



Compound	R1	X	Formula
258845	4-[(CH2)3OH]-1,4-diazoniabicyclo[2.2.2]oct-1-yl-CH2	Cl ⁻	C ₃₁ H ₃₆ ClN ₄ O ₇ S
258846	3-Me-1-imidazolyl-CH2		C ₂₆ H ₂₆ N ₄ O ₆ S
258847	3-Me-1-imidazolyl-CH2CH2		C ₂₇ H ₂₈ N ₄ O ₆ S



Compound	R1	X	Formula
258848	4-(CH ₂ CONH ₂)-1,4-diazonia-bicyclo[2.2.2]oct-1-yl-CH ₂	Cl ⁻	C ₃₀ H ₃₆ ClN ₅ O ₇ S
258849	4-(CH ₂ CONH ₂)-1,4-diazonia-bicyclo[2.2.2]oct-1-yl-CH ₂ CH ₂	Cl ⁻	C ₃₁ H ₃₈ ClN ₅ O ₇ S
258850	4-[(CH ₂) ₃ OH]-1,4-diazonia-bicyclo[2.2.2]oct-1-yl-CH ₂ CH ₂	Cl ⁻	C ₃₂ H ₄₁ ClN ₅ O ₇ S
258851	3-Me-1-imidazolyl-CH ₂ CH ₂		C ₂₇ H ₂₈ N ₄ O ₆ S

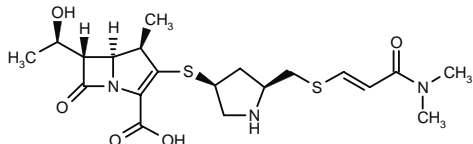
SOURCE – Merck & Co.

REFERENCES

1. Wilkening, R.R. et al. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment.* WO 9740048.

258365

(1*R*,5*S*,6*S*)-2-[[5(*S*)-[3-(*N,N*-Dimethylamino)-3-oxo-1(*E*)-propenyl]sulfanylmethyl]pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C20-H29-N3-O5-S2; Mol wt: 455.59

ACTION – Carbapenem antibacterial agent with comparable or superior antibacterial activity and greater stability to renal dehydropeptidase-I (DHP-I) compared to imipenem and meropenem. Antibacterial activity was tested *in vitro* against *Staphylococcus aureus* SG51, *Streptococcus pyogenes* A77, *Escherichia coli* O55, *Pseudomonas aeruginosa* 1771M, *Klebsiella aerogenes* 1522E and *Enterobacter cloacae* 1321E, with respective MIC values of 0.05, 0.01, 0.10, 0.10, 0.10 and 0.05 µg/ml (MIC = 0.10, 0.01, 0.20, 0.20, 0.20 and 0.05 µg/ml, respectively, for imipenem; MIC = 0.10, 0.01, 0.10, 0.10, 0.10 and 0.05 µg/ml, respectively, for meropenem); stability to DHP-I was demonstrated using porcine kidney enzyme and measuring the resistance to enzymatic degradation ($t_{1/2}$ = 516 min for title compound vs. 34 and 152 min for imipenem and meropenem, respectively). Selected for further biological evaluation.

SOURCE – Chong Kun Dang.

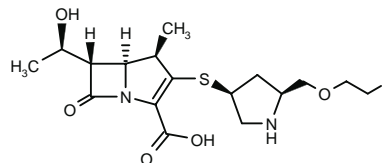
REFERENCES

1. Lee, H.-W. et al. *Synthesis and structure-activity relationship of 2-(5-substituted pyrrolidin-4-ylthio)-1β-carbapenems.* J Antibiot 1997, 50(12): 1078.

FR-27743*

156555

(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-(2-Fluoroethoxymethyl)pyrrolidin-4-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



C17-H25-F-N2-O5-S; Mol wt: 388.45

White amorphous hygroscopic solid, m.p. 155 °C (decomp.).

ACTION – Carbapenem antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa* FP 1457, *Proteus vulgaris* IAM 1025, *Klebsiella pneumoniae* 12 and *Staphylococcus aureus* 209P JC-1 (MIC = 0.78, 0.01, 0.05 and 0.1 µg/ml, respectively). It displayed good urinary recovery in rats (46% recovery after 10 mg/kg s.c.) and good stability to human renal dehydropeptidase-I (DHP-I) relative to meropenem. The compound demonstrated good *in vivo* protective effects against systemic infections in mice caused by *S. aureus* FP1469 (ED₅₀ = 0.106 mg/kg s.c.) or *P. aeruginosa* 93 (ED₅₀ = 0.537 mg/kg s.c.), being more potent than meropenem (ED₅₀ = 0.934 and 1.05 mg/kg s.c., respectively).

SOURCE – Fujisawa.

REFERENCES

1. Murata, M. et al. (Fujisawa Pharm. Co., Ltd.) *3-Pyrrolidinylthio-1-azabicyclo(3.2.0)-hept-2-en-2-carboxylic acid derivs. and their preparation.* AU 8934022, EP 341557, JP 90204490, US 4983596.

2. Azami, H. et al. *Synthesis and antibacterial activity of novel 4-pyrrolidinylthio carbapenems I. 2-Alkoxyethyl derivatives.* Bioorg Med Chem 1997, 5(11): 2069.

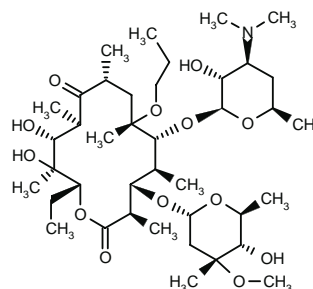
*Identified compound 156555 Drug Data Rep 1990, 12(4): 319.

MISCELLANEOUS ANTIBIOTICS

257810

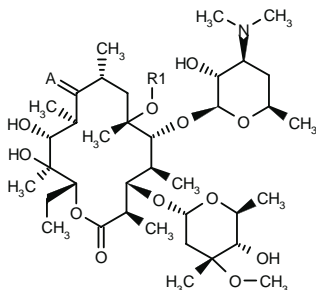
6-Deoxy-6-(propoxy)erythromycin A

6-O-Propylerythromycin



C40-H73-N-O13; Mol wt: 776.02

ACTION – Semisynthetic macrolide antibacterial agent active *in vitro* against a wide range of microorganisms such as *Staphylococcus aureus* ATCC 6538P (MIC = 3.1 µg/ml), *Streptococcus pyogenes* EES61 (MIC = 0.05 µg/ml), *Escherichia coli* SS (MIC = 1.56 µg/ml), erythromycin-resistant *Pseudomonas aeruginosa* K799/WT (MIC = 6.2 µg/ml) and *Candida albicans* CCH 442 (MIC = 0.1 µg/ml). A representative compound from a series of 6-O-substituted erythromycins, wherein the following are also included:



Compound	R1	A	Formula
258942	allyl	N(OH)	C ₄₀ H ₇₂ N ₂ O ₁₃
258943	allyl	O	C ₄₀ H ₇₁ NO ₁₃
258944	CH ₂ CH(OH)CH ₂ OH	O	C ₄₀ H ₇₃ NO ₁₅
258945	1-imidazolyl-CH ₂ CH(OH)CH ₂	O	C ₄₃ H ₇₅ N ₃ O ₁₄
258946	4-morpholinyl-CH ₂ CH(OH)CH ₂	O	C ₄₄ H ₈₀ N ₂ O ₁₅
258947	CH ₂ CH(OH)CH ₂ NHCH ₂ Ph	O	C ₄₇ H ₈₀ N ₂ O ₁₄
258948	CH ₂ CHO	O	C ₃₉ H ₆₉ NO ₁₄
258949	CH ₂ Ac	O	C ₄₀ H ₇₁ NO ₁₄
258950	ethynyl-CH ₂	O	C ₄₀ H ₆₉ NO ₁₃
258951	CH ₂ CH(OH)CH ₂ N ₃	O	C ₄₀ H ₇₂ N ₄ O ₁₄
258952	CH ₂ CH=NOH	O	C ₃₉ H ₇₀ N ₂ O ₁₄

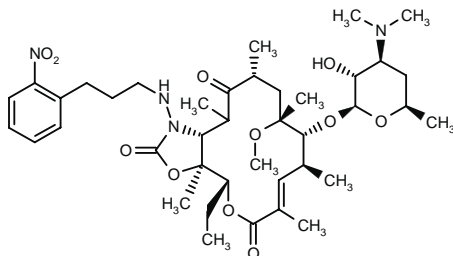
SOURCE – Abbott.

REFERENCES

1. Or, Y.S. et al. (Abbott Labs.) *6-O-Substd. erythromycins and method for making them*. WO 9742204, WO 9742206.

257811

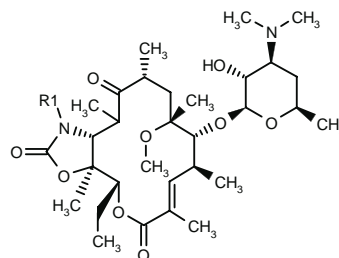
3-Des(hexopyranosyloxy)-11-desoxy-6-*O*-methyl-11-[*N*²-[3-(2-nitrophenyl)propyl]hydrazino]-2,3-didehydroerythromycin A 11-*N*¹,12-*O*-cyclic carbamate



C40-H62-N4-O11; Mol wt: 774.95

ACTION – Semisynthetic macrolide antibacterial agent active *in vitro* against a broad range of microorganisms including *Staphylococcus aureus* ATCC 6538P (MIC = 0.1 µg/ml), *Enterococcus faecium* ATCC 8043 (MIC = 0.01 µg/ml), *Streptococcus pyogenes* EES61 (MIC = 0.005 µg/ml) and *Escherichia coli* SS (MIC = 0.2 µg/ml), being slightly more potent than erythromycin A (MIC = 0.2, 0.1,

0.02 and 0.39 $\mu\text{g/ml}$, respectively). A representative compound from a series of 3-descladinose-2,3-anhydroerythromycin derivatives, wherein the following are also included:



Compound	R1	Formula
259057	NH(CH ₂) ₃ Ph	C ₄₀ H ₆₃ N ₃ O ₉
259058	4-NO ₂ -PhCH ₂ CH ₂	C ₃₉ H ₅₉ N ₃ O ₁₁
259059	4-Cl-Ph(CH ₂) ₃	C ₄₀ H ₆₁ ClN ₂ O ₉
259060	4-OH-Ph(CH ₂) ₃ NH	C ₄₀ H ₆₃ N ₃ O ₁₀
259061	3-OH-Ph(CH ₂) ₃ NH	C ₄₀ H ₆₃ N ₃ O ₁₀

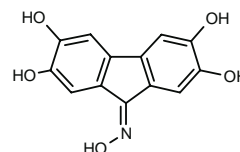
SOURCE – Abbott.

REFERENCES

1. Elliott, R.L. et al. (Abbott Labs.) *3-Descladinose-2,3-anhydroerythromycin derivs.*
WO 9742205.

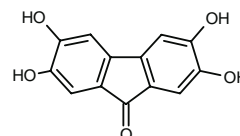
MISCELLANEOUS ANTIBACTERIAL DRUGS

258527

2,3,6,7-Tetrahydroxy-9*H*-fluoren-9-one oxime

C13-H19-N-O5; Mol wt: 269.30

ACTION – Potential antibacterial agent, a tricyclic analog of ellagic acid found to inhibit *Escherichia coli* DNA gyrase supercoiling with an IC_{50} of 2 $\mu\text{g/ml}$. Another related compound with similar activity ($IC_{50} = 13 \mu\text{g/ml}$) in the same assay is:



258868: C13-H8-O5

SOURCE – R.W. Johnson Pharm. Res. Inst.

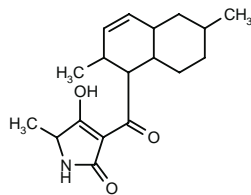
REFERENCES

1. Weidner-Wells, M.A. et al. *DNA gyrase inhibitory activity of ellagic acid derivatives*. Bioorg Med Chem Lett 1998, 8(1): 97.

F-12434

256428

3-(2,6-Dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-ylcarbonyl)-4-hydroxy-5-methyl-2,5-dihydro-1*H*-pyrrol-2-one



C18-H25-N-O3; Mol wt: 303.40

ACTION – Antibacterial agent isolated from *Dicephalospora rufocornea* Spooner SANK 27795 (FERM BP-5364), active against Gram-positive bacteria such as *Staphylococcus aureus* 209P, *S. aureus* 56R, methicillin-resistant *S. aureus* 535 and *Enterococcus faecalis* 681, with MIC values of 6.2, 6.2, 6.2 and 12.5 µg/ml, respectively.

SOURCE – Sankyo.

REFERENCES

1. Hosoya, T. and Takahashi, H. (Sankyo Co., Ltd.) *Novel cpd. F-12434*. JP 97227514.

HUMAN CYSTATIN F

257188

ACTION – Agent for the treatment of bacterial and viral infections, immunological disorders and inflammation, a novel human polypeptide of the cystatin superfamily, which comprises a group of cysteine protease inhibitors that form tight and reversible complexes with cysteine proteases such as cathepsins B, H, L and S. Also disclosed is the use of antibodies against this peptide in the diagnosis of hereditary cystatin C amyloidosis angiopathy (HCCAA) and neoplasia, as well as the use of antagonists in the treatment or prevention of cerebral hemorrhage, encephalopathy, HIV infection and tumors.

SOURCE – Human Genome Sciences.

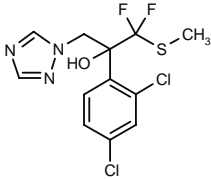
REFERENCES

1. Ni, J. et al. (Human Genome Sci., Inc.) *Human cystatin F*. WO 9737021.

ANTIFUNGAL AGENTS

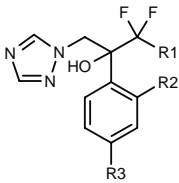
256431

2-(2,4-Dichlorophenyl)-1,1-difluoro-1-(methylsulfanyl)-3-(1,2,4-triazol-1-yl)-2-propanol



C12-H11-Cl2-F2-N3-O-S; Mol wt: 354.20

ACTION – Oral antifungal agent with potent activity against *Candida albicans* ATCC 44859 (MIC = 3.9 ng/ml) and *Aspergillus fumigatus* IFM 40808 (MIC = 2 µg/ml). Within this series of triazole derivatives, the following are also included:



Compound	R1	R2	R3	Isomer	Formula
258093	SO2Me	F	F	(-)	C ₁₂ H ₁₁ F ₄ N ₃ O ₃ S
258094	SMe	F	F		C ₁₂ H ₁₁ F ₄ N ₃ OS
258095	SO2Me	Cl	Cl	(-)	C ₁₂ H ₁₁ Cl ₂ F ₂ N ₃ O ₃ S
258096	SMe	H	CF3		C ₁₃ H ₁₂ F ₃ N ₃ OS

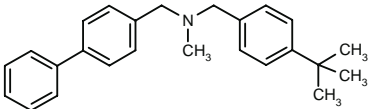
SOURCE – SS Pharm.

REFERENCES

1. Tokizawa, M. et al. (SS Pharm. Co., Ltd.) *Triazole derivs., the preparation method thereof and the medicinals containing the same as effective ingredient*. JP 97227531.

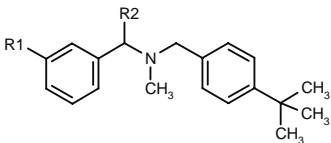
256461

N-(Biphenyl-4-ylmethyl)-*N*-(4-*tert*-butylbenzyl)-*N*-methylamine



C25-H29-N; Mol wt: 343.51

ACTION – Antifungal agent active *in vitro* against *Trichophyton mentagrophytes* TIMM1189 (MIC = 12.5 µg/ml). Within this series of benzylamine derivatives, the following are also included:



Compound	R1	R2	Formula
258234	Ph	H	C ₂₅ H ₂₉ N
258235	H	Ph	C ₂₅ H ₂₉ N

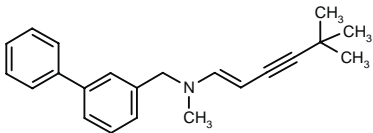
SOURCES – Pola.

REFERENCES

1. Kawazu, Y. et al (Pola Chem. Ind., Inc.) *Antifungal agents*. JP 97255633.

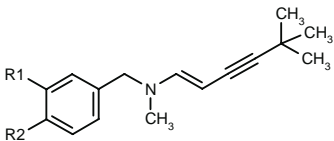
256462

N-(Biphenyl-3-ylmethyl)-N-[5,5-dimethylhex-1(E)-en-3-ynyl]-N-methylamine



C22-H25-N; Mol wt: 303.45

ACTION – Antifungal agent active *in vitro* against *Trichophyton mentagrophytes* TIMM1189 (MIC = 12.5 µg/ml). Other representative compounds within this series of benzylamine derivatives include the following:



Compound	R1	R2	Isomer	Formula
258236	H	H	E	C ₂₂ H ₂₅ N
258237	Ph	H	Z	C ₂₂ H ₂₅ N
258238	H	Ph	E	C ₂₂ H ₂₅ N

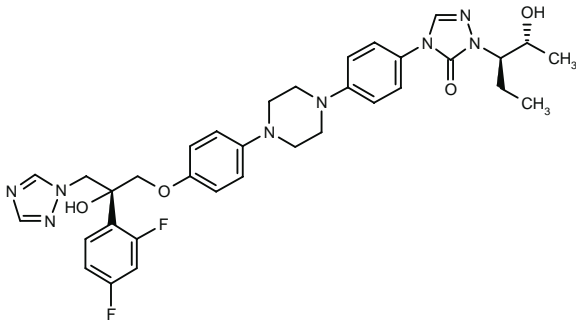
SOURCE – Pola.

REFERENCES

1. Yuasa, M. et al. (Pola Chem. Ind., Inc.) *Antifungal agents*. JP 97255634.

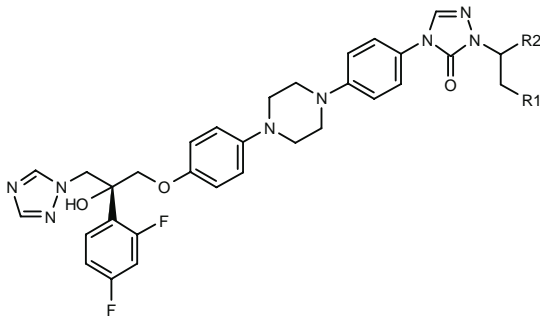
257850

4-[4-[4-[4-[2(R)-(2,4-Difluorophenyl)-2-hydroxy-3-(1,2,4-triazol-1-yl)propoxy]phenyl]piperazin-1-yl]phenyl]-2-[1(R)-ethyl-2(R)-hydroxypropyl]-3,4-dihydro-2H-1,2,4-triazol-3-one



C34-H38-F2-N8-O4; Mol wt: 660.72

ACTION – Triazole antifungal agent reported to possess a broad spectrum of activity against pathogens such as *Aspergillus*, *Blastomyces*, *Candida*, *Cryptococcus*, *Coccidioides*, *Epidermophyton*, *Trichophyton* and *Pneumocystis*. Other hydroxy-substituted antifungals include the following:



Compound	R1	R2	Isomer	Formula
258053	Me	(S)-CH(OH)Me	S	C ₃₄ H ₃₈ F ₂ N ₈ O ₄
258054	Me	(S)-CH(OH)Me	R	C ₃₄ H ₃₈ F ₂ N ₈ O ₄
258055	Me	(R)-CH(OH)Me	S	C ₃₄ H ₃₈ F ₂ N ₈ O ₄
258056	Me	CH ₂ CH ₂ OH	R	C ₃₄ H ₃₈ F ₂ N ₈ O ₄
258057	Me	CH ₂ CH ₂ OH	S	C ₃₄ H ₃₈ F ₂ N ₈ O ₄
258058	H	(R)-CH(OH)Me	R	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258059	H	(R)-CH(OH)Me	S	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258060	H	(S)-CH(OH)Me	R	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258061	H	(S)-CH(OH)Me	S	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258062	H	CH ₂ CH ₂ OH	R	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258063	H	CH ₂ CH ₂ OH	S	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258064	Me	CH ₂ OH	R	C ₃₃ H ₃₆ F ₂ N ₈ O ₄
258065	Me	CH ₂ OH	S	C ₃₃ H ₃₆ F ₂ N ₈ O ₄

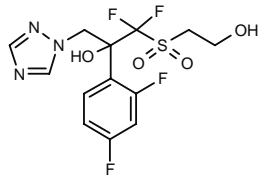
SOURCE – Schering-Plough.

REFERENCES

1. Saksena, A.K. et al. (Schering Corp.) *Hydroxy-substd. antifungals*. US 5698557.

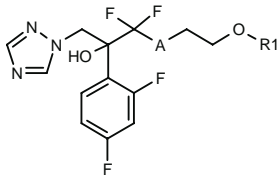
258742

2-(2,4-Difluorophenyl)-1,1-difluoro-1-(2-hydroxyethylsulfonyl)-3-(1,2,4-triazol-1-yl)-2-propanol



C13-H13-F4-N3-O4-S; Mol wt: 383.32

ACTION – Orally active triazole antifungal agent reported to possess excellent activity against *Aspergillus* spp. and *Candida* spp. *In vivo* activity was demonstrated in a murine model of systemic candidosis, where no mortality was observed 14 days after infection at a dose of 1.25 mg/kg p.o. at 1 and 24 h postinfection followed by daily treatment for the next 4 days, compared to 100% mortality with fluconazole at the same dose. Other compounds from this series of triazole derivatives include the following:



Compound	R1	A	Formula
259235	Ac	S	C ₁₅ H ₁₅ F ₄ N ₃ O ₃ S
259236	Me	S	C ₁₄ H ₁₅ F ₄ N ₃ O ₂ S
259237	H	S	C ₁₃ H ₁₃ F ₄ N ₃ O ₂ S
259238	Me	SO ₂	C ₁₄ H ₁₅ F ₄ N ₃ O ₄ S

SOURCE – SS Pharm.

REFERENCES

1. Tokizawa, M. et al. (SS Pharm. Co., Ltd.) *Triazole deriv. or salt thereof*. EP 814079.

TKR-842

256460

ACTION – Antifungal antibiotic produced by culturing the microorganism *Chalara* sp. TKR 842 (FERM P-15474), proven active against *Cryptococcus neoformans* TIMM 0354 (MIC = 25 µg/ml) and *Aspergillus fumigatus* TIMM 1776 (MIC = 25 µg/ml).

SOURCE – Takara Shuzo.

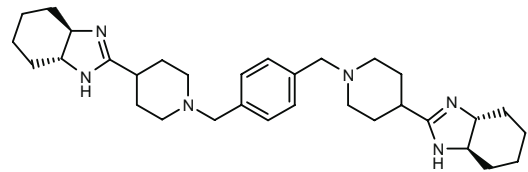
REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Antibiotic TKR842 and the preparation method thereof*. JP 97249680.

ANTIVIRAL DRUGS

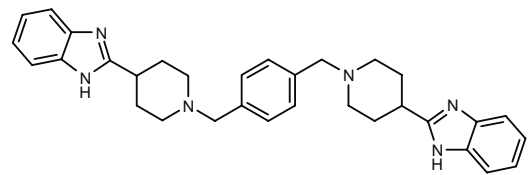
257134

trans-1,1'-(1,4-Phenylene)bis(methylene)bis[4-(3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazol-2-yl)piperidine]



C32-H48-N6; Mol wt: 516.77

ACTION – Antiviral agent for the treatment or prophylaxis of hepatitis C virus (HCV) infections. Compound was shown *in vitro* to inhibit viral helicase activity (IC₅₀ = 7 µM), suggesting that it interferes with HCV replication. Another specifically claimed piperidine derivative is:



257613: C32-H36-N6

SOURCE – Viropharma.

REFERENCES

1. Diana, G.D. et al. (Viropharma, Inc.) *Piperidine derivs., pharmaceutical compsns. thereof and their use in the treatment of hepatitis C*. WO 9736554.

257201

Antisense 20-mer single-stranded phosphorothioate oligonucleotide whose nucleotide sequence is: 5'-TTTGGGTCTCTCTTTGGGTC-3'

ACTION – Antiviral antisense oligonucleotide against Epstein-Barr virus (EBV) targeting the *BZLF1* gene generally associated with the viral lytic cycle. At 25 µM, test compound inhibited linear EBV DNA synthesis by 57%. Also included in the invention are antisense oligonucleotides targeting EBV gene sequences generally associated with the viral latent cycle.

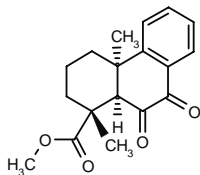
SOURCE – Univ. Massachusetts, Boston, MA (US).

REFERENCES

1. Mulder, C. (Univ. Massachusetts) *Oligonucleotides with anti-Epstein-Barr virus activity*. WO 9737669.

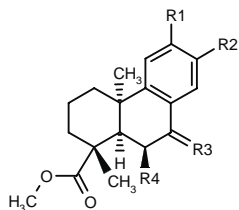
257793

[1*R*-(1 α ,4 α ,10 α)]-1,4a-Dimethyl-9,10-dioxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid methyl ester



C₁₈H₂₀O₄; Mol wt: 300.35

ACTION – Antiviral agent that inhibits the replication of influenza and other enveloped viruses by inhibiting hemagglutinin-mediated fusion of virus with the host cell. In a plaque reduction assay, it gave IC₅₀ values of 0.01-5.9 µg/ml against influenza A/Kawasaki and of 3.3-19 µg/ml against influenza B/Lee. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
258919	H	H	O	Br	C ₁₈ H ₂₁ BrO ₃
258920	H	H	O	H	C ₁₈ H ₂₂ O ₃
258921	H	H	-N(OH)-	H	C ₁₈ H ₂₃ NO ₃
258922	H	H	-N(OCH ₂ CO ₂ Me)-	H	C ₂₁ H ₂₇ NO ₅
258923	H	H	-N(OCH ₂ CO ₂ H)-	H	C ₂₀ H ₂₅ NO ₅
258924	H	H	-(NOCH ₂ CO ₂ Na)-	H	C ₂₀ H ₂₄ NNaO ₅
258925	OMe	H	-N(OH)-	H	C ₁₉ H ₂₅ NO ₄
258926	H	OMe	-N(OH)-	H	C ₁₉ H ₂₅ NO ₄

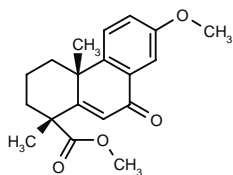
SOURCE – Lilly.

REFERENCES

1. Mauldin, S.C. and Munroe, J.E. (Eli Lilly & Co.) *Anti-viral cpds.* WO 9741860.

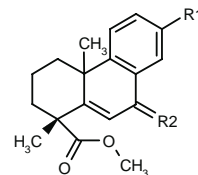
257794

[1*R*-(1 α ,4 α)]-7-Methoxy-1,4a-dimethyl-9-oxo-1,2,3,4,4a,9-hexahydrophenanthrene-1-carboxylic acid methyl ester



C₁₉H₂₂O₄; Mol wt: 314.38

ACTION – Antiviral agent for the treatment of influenza and other enveloped virus infections that acts by inhibiting the hemagglutinin-mediated fusion of the virus with the host cell. Using a plaque reduction assay, compound was found to exhibit an IC₅₀ value in the range of 0.54-6.4 µg/ml against influenza A/Kawasaki. Other related compounds include the following:



Compound	R1	R2	Isomer	Formula
258835	OMe	-N(OH)-	R	C ₁₉ H ₂₃ NO ₄
258836	H	O	R	C ₁₈ H ₂₀ O ₃
258837	H	-N(OH)-	R	C ₁₈ H ₂₁ NO ₃
258838	H	O	S	C ₁₈ H ₂₀ O ₃
258839	H	-N(OH)-	S	C ₁₈ H ₂₁ NO ₃

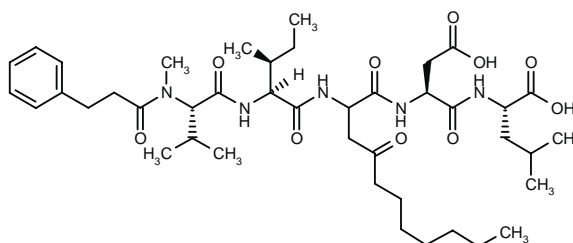
SOURCE – Lilly.

REFERENCES

1. Mauldin, S.C. and Munroe, J.E. (Eli Lilly & Co.) *Anti-viral cpds.* EP 806409, WO 9741861

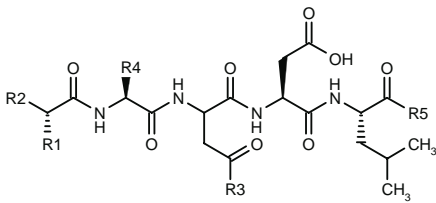
258209

3-Phenylpropionyl-L-(*N*-methyl)valyl-L-isoleucyl-(2-amino-4-oxoundecanoyl)-L-aspartyl-L-leucine

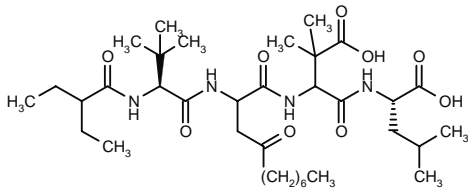


C₄₂H₆₇N₅O₁₀; Mol wt: 802.02

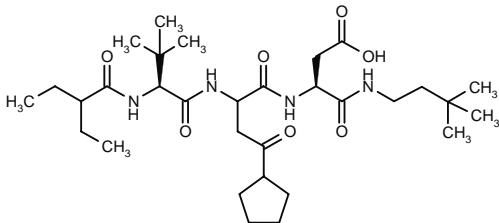
ACTION – Antiviral agent for the treatment of herpesvirus infections with potent inhibitory activity against herpes simplex virus type 1 (HSV-1) ribonucleotide reductase (IC₅₀ = 0.42 µM). A representative compound from a series of specifically claimed peptides having a 2-oxoalkyl amino acid side-chain, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
258275	i-Pr	N(Me)CO-CH2CH2Ph	cyclopentyl	(S)-CH(Me)Et	OH	C ₄₀ H ₆₁ N ₅ O ₁₀
258276	i-Pr	N(Me)CO-CH2CH2Ph	C11H23	(S)-CH(Me)Et	NH2	C ₄₆ H ₇₆ N ₆ O ₉
258277	Et	Et	C11H23	(S)-CH(Me)Et	OH	C ₃₇ H ₆₆ N ₄ O ₉
258278	i-Pr	N(Me)CO-CH2CH2Ph	Me	(S)-CH(Me)Et	OH	C ₃₆ H ₅₆ N ₅ O ₁₀
258279	Et	Et	C7H15	(S)-CH(Me)Et	OH	C ₃₃ H ₅₈ N ₄ O ₉
258280	Et	Et	C5H11	t-Bu	OH	C ₃₁ H ₅₄ N ₄ O ₉
258281	Et	Et	C7H15	t-Bu	OH	C ₃₃ H ₅₈ N ₄ O ₉



258282: C35-H62-N4-O9



258283: C31-H54-N4-O7

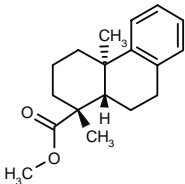
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Beaulieu, P.L. et al. (Boehringer Ingelheim [Canada], Ltd.) *Antiviral peptide derivs. having a 2-oxoalkyl amino acid side chain*. US 5700780.

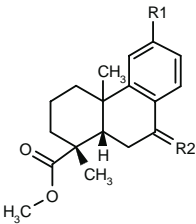
258719

(1*R*,4*aR*,10*aS*)-1,4*a*-Dimethyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-1-carboxylic acid methyl ester



C18-H24-O2; Mol wt: 272.39

ACTION – Antiviral agent for the treatment of influenza and other enveloped virus infections that acts by inhibiting the hemagglutinin-mediated fusion of the virus with the host cell. Using a plaque reduction assay, compound was found to exhibit an IC₅₀ value in the range 0.01-0.65 µg/ml against influenza A/Kawasaki and 1.6-10 µg/ml against influenza B/Lee. Other related compounds include the following:



Compound	R1	R2	Isomer	Formula
259246	H	O	R	C ₁₈ H ₂₂ O ₃
259247	H	O	S	C ₁₈ H ₂₂ O ₃
259248	H	-N(OH)-	R	C ₁₈ H ₂₃ NO ₃
259249	OMe	O	R	C ₁₉ H ₂₄ O ₄
259250	OMe	-N(OH)-	R	C ₁₉ H ₂₅ NO ₄

SOURCE – Lilly.

REFERENCES

1. Mauldin, S.C. and Munroe, J.E. (Eli Lilly & Co.) *Anti-viral cpds*. EP 811600.

FR-198248

256459

ACTION – Antiviral agent isolated from the culture of *Aspergillus terreus* No. 13830 (FERM BP-5371), proven to induce 100% inhibition of influenza virus A/PR/8/34 replication at a concentration of 10 µg/ml in a plaque formation assay.

SOURCE – Fujisawa.

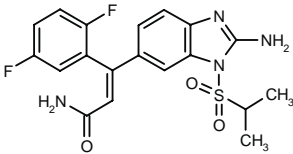
REFERENCES

1. Nishihara, Y. et al. (Fujisawa Pharm. Co., Ltd.) *FR198248 substance*. JP 97249679.

LY-354400

255577

(*Z*)-3-[2-Amino-1-(isopropylsulfonyl)benzimidazol-6-yl]-3-(2,5-difluorophenyl)-2-propenamide



C19-H18-F2-N4-O3-S; Mol wt: 420.43

ACTION – Antiviral agent, an orally active benzimidazole derivative with potent, broad-spectrum activity against rhinoviruses/enteroviruses (IC₅₀ = 0.027-0.15 µg/ml). In rats administered an oral dose of 300 mg/kg, it gave a C_{max} of 9.9 µg/ml, with no apparent toxicity. Compound was selected as a lead for further development.

SOURCE – Lilly.

REFERENCES

1. Jungheim, L.N. et al. (Eli Lilly & Co.) *Anti-viral cpds.* WO 9746235.

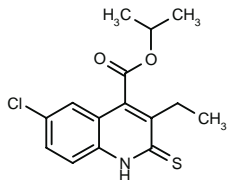
2. Tebbe, M.J. et al. *Toxicological studies of the vinyl carboxamide benzimidazoles: Selection of LY354400 as a lead candidate.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst H-143.

3. Tebbe, M. *Potent, broad spectrum, antirhino/enterovirals related to enviroxime: A new generation of benzimidazoles.* IBC Conf Antivir. Latest Preclin Clin Dev Infect Dis (June 26-27, Washington DC) 1997.

AIDS MEDICINES

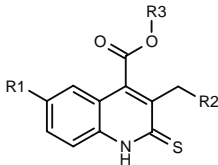
257210

6-Chloro-3-ethyl-2-thioxo-1,2-dihydroquinoline-4-carboxylic acid isopropyl ester



C15-H16-Cl-N-O2-S; Mol wt: 309.81

ACTION – Antiviral agent for AIDS active against HIV in infected lymphocytes (EC₅₀ approx. 2 ng/ml); it acts by inhibiting reverse transcriptase (IC₅₀ = 0.008 μM). Within this series of substituted quinoline derivatives, the following are also included:



Compound	R1	R2	R3	Formula
258173	H	H	Me	C ₁₂ H ₁₁ NO ₂ S
258174	Cl	H	i-Pr	C ₁₄ H ₁₄ ClNO ₂ S
258175	Cl	Me	Et	C ₁₄ H ₁₄ ClNO ₂ S
258176	Cl	Me	allyl	C ₁₅ H ₁₄ ClNO ₂ S

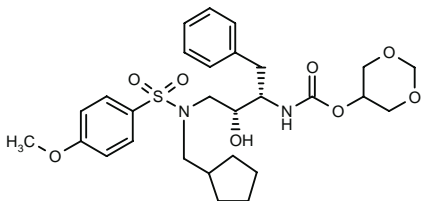
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Kirsch, R. et al. (Hoechst AG) *Substd. quinoline derivs. with antiviral action.* DE 19613591, WO 9737977.

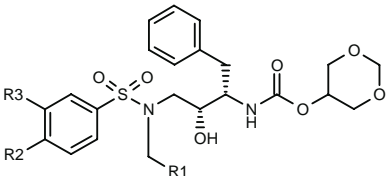
257268

N-[1(S)-Benzyl-3-[N-(cyclopentylmethyl)-4-methoxyphenylsulfonamido]-2(R)-hydroxypropyl]carbamic acid 1,3-dioxan-5-yl ester



C28-H38-N2-O8-S; Mol wt: 562.68

ACTION – Antiviral agent for AIDS, an inhibitor of aspartyl proteases, particularly HIV-1 (K_i < 0.10 nM) and HIV-2 aspartyl proteases. Antiviral activity was demonstrated by inhibition of HIV_{IIIb} replication in CCRM-CEM cells (IC₉₀ = 5 nM). It is reported to be orally bioavailable and to possess an extremely high therapeutic index. Other compounds from this series of oxygenated heterocycle-containing sulfonamides include the following:



Compound	R1	R2	R3	Formula
258127	cyclopentyl	NH2	H	C ₂₇ H ₃₇ N ₃ O ₇ S
258128	i-Pr	NH2	H	C ₂₈ H ₃₈ N ₃ O ₇ S
258129	cyclopentyl	H	NH2	C ₂₇ H ₃₇ N ₃ O ₇ S

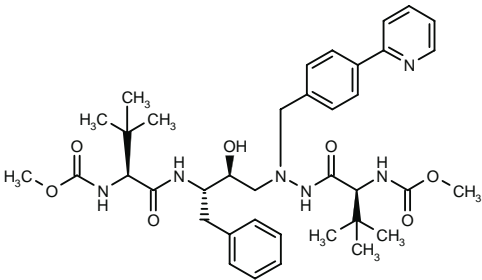
SOURCE – Vertex.

REFERENCES

1. Tung, R.D. and Bhisetti, G.R. (Vertex Pharm., Inc.) *Oxygenated-heterocycle containing sulfonamide inhibitors of aspartyl protease.* US 5691372.

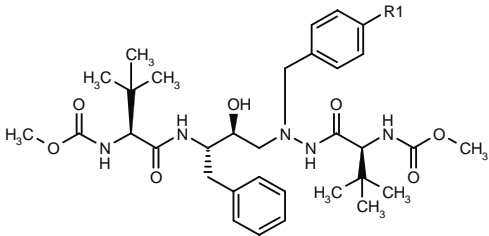
257722

N'-[2(S)-Hydroxy-3(S)-(methoxycarbonyl-L-tert-leucyl-amino)-4-phenylbutyl]-N^α-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L-tert-leucylhydrazide



C38-H52-N6-O7; Mol wt: 704.86

ACTION – Antiviral agent for AIDS, an inhibitor of HIV-1 protease (IC₅₀ = 0.019 μM) found to protect MT-2 cells against HIV-1 infection with an ED₉₀ of 0.003 μM. After a dose of 120 mg/kg p.o. in mice, blood levels of test compound were 21.83 μM at 30 min and 31.76 μM at 90 min. Other representative compounds within this series of heterocyclic azahexane derivatives include the following:



Compound	R1	Formula
258681	5-thiazolyl	C ₃₆ H ₅₀ N ₆ O ₇ S
258682	2-Me-5-tetrazolyl	C ₃₆ H ₅₁ N ₉ O ₇

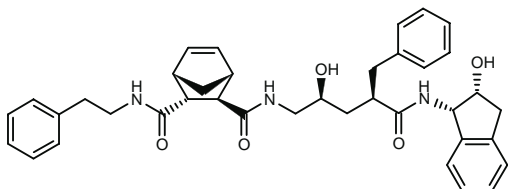
SOURCE – Novartis.

REFERENCES

1. Fässler, A. et al. (Novartis AG) *Antivirally active heterocyclic azahehexane derivs.* WO 9740029.

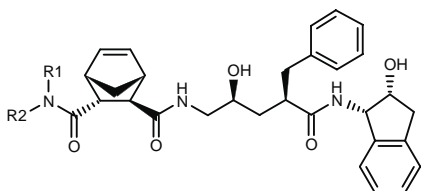
257744

(1*R*,2*R*,3*R*,4*S*)-*N*²-[4(*R*)-Benzyl-2(*S*)-hydroxy-4-[*N*-[2(*R*)-hydroxyindan-1(*S*)-yl]carbamoyl]butyl]-*N*³-(2-phenylethyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide



C38-H43-N3-O5; Mol wt: 621.77

ACTION – Antiviral agent for AIDS that acts by inhibiting HIV protease (IC₅₀ = 0.055 nM). Other specifically claimed compounds from this series of norbornene derivatives include the following:



Compound	R1	R2	Formula
258852	t-Bu	H	C ₃₄ H ₄₃ N ₃ O ₅
258853	CH ₂ Ph	CH ₂ Ph	C ₄₄ H ₄₇ N ₃ O ₅

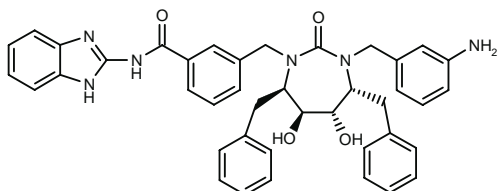
SOURCE – Merck & Co.

REFERENCES

1. Hungate, R.W. et al. (Merck & Co., Inc.) *HIV protease inhibitors useful for the treatment of AIDS.* WO 9740825.

258690

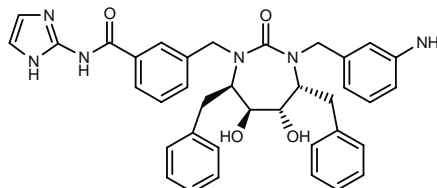
(4*R*,5*S*,6*S*,7*R*)-3-[3-(3-Aminobenzyl)-4,7-dibenzyl-5,6-dihydroxy-2-oxoperhydrodiazepin-1-ylmethyl]-*N*-(2-benzimidazole)benzamide



C41-H40-N6-O4; Mol wt: 680.80

M.p. 135 °C (decomp.).

ACTION – Antiviral agent for AIDS, a nonsymmetrically substituted cyclic urea with more potent HIV protease-inhibitory and antiviral activity (K_i = 0.023 nM; IC₉₀ [concentration required to inhibit HIV RNA synthesis by 90%] = 13.2 nM) than DMP-450 (K_i = 0.31 nM; IC₉₀ = 125.0 nM), with excellent oral bioavailability and a pharmacokinetic profile in dogs that compares favorably with DMP-450. Presently under further investigation along with the following related compound:



258691: C37-H38-N6-O4

SOURCE – DuPont Merck.

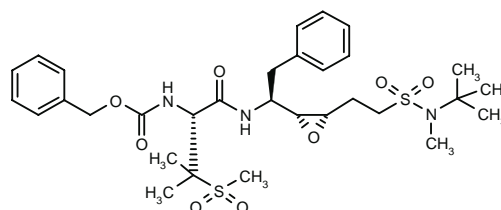
REFERENCES

1. Jadhav, P.K. (E.I. Du Pont De Nemours & Co.) *Cyclic urea HIV protease inhibitors.* US 5683999, WO 9629329.

2. Wilkerson, W.W. et al. *Nonsymmetrically substituted cyclic urea HIV protease inhibitors.* J Med Chem 1997, 40(25): 4079.

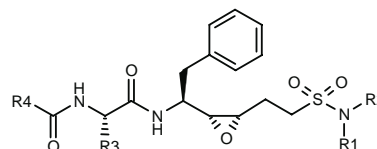
258733

(3*S*,4*R*,5*S*)-5-[*N*-(Benzyloxycarbonyl)-3-(methanesulfonyl)-L-valylamino]-*N*-*tert*-butyl-3,4-epoxy-*N*-methyl-6-phenylhexanesulfonamide



C31-H45-N3-O8-S2; Mol wt: 651.83

ACTION – Antiviral agent for AIDS, an irreversible inhibitor of HIV-1 protease with potent anti-HIV-1 activity (IC₅₀ = 1 nM) and low cytotoxicity (CT₅₀ > 10 μM in uninfected cells). A representative compound from a series of specifically claimed *cis*-epoxide derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
259214	t-Bu	H	C(Me)2SO ₂ Me	OCH ₂ Ph	C ₃₀ H ₄₃ N ₃ O ₈ S ₂
259215	t-Bu	H	C(Me)2SO ₂ Me	2-quinoliny	C ₃₂ H ₄₂ N ₄ O ₇ S ₂
259216	t-Bu	H	CH ₂ CONH ₂	2-quinoliny	C ₃₀ H ₃₇ N ₅ O ₆ S
259217	t-Bu	Me	C(Me)2SO ₂ Me	5-isoquinolyl-OCH ₂	C ₃₄ H ₄₆ N ₄ O ₈ S ₂
259218	Ph	Et	C(Me)2SO ₂ Me	2-quinoliny	C ₃₆ H ₄₂ N ₄ O ₇ S ₂
259219	Ph	Et	CH ₂ CONH ₂	2-quinoliny	C ₃₄ H ₃₇ N ₅ O ₆ S
259221	CH(<i>i</i> -Pr) ₂	H	C(Me)2SO ₂ Me	OCH ₂ Ph	C ₃₃ H ₄₉ N ₃ O ₈ S ₂

SOURCE – LG Chemical.

REFERENCES

1. Choy, N. et al. (LG Chem., Ltd.) *Irreversible HIV protease inhibitors, compsns. containing same and process for the preparation thereof*. EP 812857.

LAMIVUDINE/ZIDOVUDINE

New combination

258524

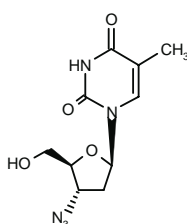
Fixed combination of lamivudine and zidovudine

Zidovudine

Rec INN; BAN; USAN

113563

3'-Azido-3'-deoxythymidine



C10-H13-N5-O4; Mol wt: 267.24

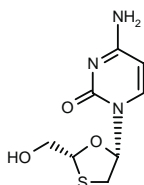
Lamivudine

Rec INN; BAN; USAN

184356

(–)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

(–)-(2'*R*,5'*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine



C8-H11-N3-O3-S; Mol wt: 229.25

ACTION – Combination of antiretroviral nucleoside analogues in a single tablet.

INDICATION – Treatment of HIV infection.

PRESENTATION – Tablets, 150 mg lamivudine/300 mg zidovudine.

PROPRIETARY NAME – *Combivir* (US).

SOURCE – Glaxo Wellcome.

REFERENCES

1. Eron, J. et al. *Combivir™, a fixed formulation of lamivudine (3TC) 150 mg and zidovudine (ZVD) 300 mg, given BID plus a protease inhibitor (PI) compared to 3TC 150 mg BID and ZVD 200 mg TID plus a PI*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 387c.

2. Moore, K.H.P. et al. *Bioequivalence of Combivir™ tablet and Epivir® plus Retrovir® tablets*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 671.

3. Vesanen, M. et al. *HIV-1 viral kinetics in gut-associated-lymphoid-tissue (GALT) in chronically infected patients treated with combination therapy*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 518.

4. *Combivir recommended for approval in Europe*. Prous Science Daily Essentials November 24, 1997.

5. *COMBIVIR™ Tablets*. Glaxo Wellcome Product Insert 1997, September.

6. *First combination anti-HIV drug approved in U.S.* Prous Science Daily Essentials September 30, 1997.

7. *First tablet to combine two anti-HIV drugs cleared for use in the USA*. Glaxo Wellcome plc Press Release 1997, September 29.

8. *Zidovudine/lamivudine launch*. Glaxo Wellcome plc Company Communication 1997, November 17.

TREATMENT OF PROTOZOAL DISEASES

ATOVAQUONE/PROGUANIL HYDROCHLORIDE

New combination

258518

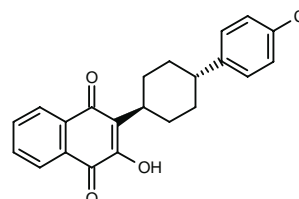
Fixed combination of atovaquone and proguanil hydrochloride

Atovaquone

Rec INN; BAN; USAN

159885

2-[*trans*-4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone



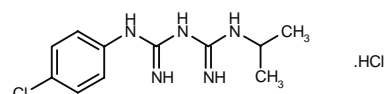
C22-H19-Cl-O3; Mol wt: 366.84

Proguanil Hydrochloride

Rec INN; BAN; JAN

258517

1-(4-Chlorophenyl)-5-isopropylbiguanide hydrochloride



C11-H16-Cl-N5.HCl; Mol wt: 290.19

ACTION – Antiprotozoal combination.

INDICATION – Treatment of acute, uncomplicated *Plasmodium falciparum* malaria where the pathogen is likely to be resistant to other antimalarial agents.

PRESENTATION – Tablets, 250 mg atovaquone/100 mg proguanil hydrochloride.

PROPRIETARY NAME – *Malarone* (CH, GB).

SOURCE – Glaxo Wellcome.

REFERENCES

1. Hutchinson, D.B.A. *Overview of Malarone - a fixed dose combination of atovaquone and proguanil - for the treatment and prophylaxis of malaria*. 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-84-1.

2. Lell, B. et al. *A randomized, double-blind, placebo-controlled study to evaluate the suppressive prophylactic activity of atovaquone plus proguanil (Malarone™) in children at risk of developing Plasmodium falciparum infection.* Amer J Trop Med Hyg 1997, 57 (3, Suppl.): Abst 8.

3. Radloff, P.D. et al. *Atovaquone and proguanil for Plasmodium falciparum malaria.* Lancet 1996, 347: 1511.

4. Sabchareon, A. et al. *Uncontrolled clinical trial of a combination of atovaquone and proguanil in the treatment of acute P. falciparum malaria in children in Thailand.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst P-01-116.

5. Shanks, D. et al. *A randomized, double-blinded, placebo-controlled field trial of the chemosuppressive activity of atovaquone/proguanil (Malarone®) for P. falciparum in Kenya.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-84-2.

6. *Glaxo Wellcome development pipeline.* Prous Science Daily Essentials February 28, 1997.

7. *Malarone launch.* Glaxo Wellcome Company Communication 1997, October 14.

8. *New antimalarial combination launched this week in second market.* Prous Science Daily Essentials October 14, 1997.

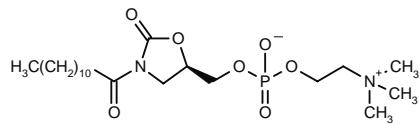
9. *U.K. launch for Malarone, a potent new antimalarial combination.* Prous Science Daily Essentials November 3, 1997.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

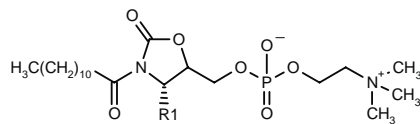
256450

Phosphocholine 3-(dodecanoyl)-2-oxooxazolidin-5(R)-yl-methyl monoester



C21-H41-N2-O7-P; Mol wt: 464.54

ACTION – Antiinflammatory and antiallergic agent, an inhibitor of phospholipase A₂ (PLA₂). Within this series of oxazolidinone derivatives, the following are also included:



Compound	R1	Isomer	Formula
258230	Pr	5S	C ₂₄ H ₄₇ N ₂ O ₇ P
258231	Pr	5R	C ₂₄ H ₄₇ N ₂ O ₇ P
258232	H	5S	C ₂₁ H ₄₁ N ₂ O ₇ P

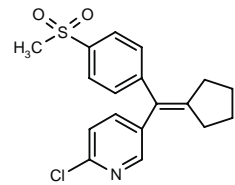
SOURCE – Santen.

REFERENCES

1. Katsumura, N. (Santen Pharm. Co., Ltd.) *Oxazolidinone derivs.* JP 97241278.

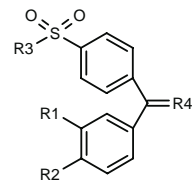
256659

2-Chloro-5-[1-cyclopentylidene-1-[4-(methylsulfonyl)-phenyl]methyl]pyridine



C18-H18-Cl-N-O2-S; Mol wt: 347.86

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; 65% inhibition at 10 μM vs. 0% inhibition of COX-1 at 10 μM using purified sheep enzymes). *In vivo* activity was demonstrated in rats in the carrageenan-induced paw edema test (45.8 ± 9.8% inhibition at 100 mg/kg p.o.) and in the kaolin-induced arthritis test (55.0 ± 15.7% inhibition at 100 mg/kg p.o.). A representative compound from a series of specifically claimed carbocyclic diaryl methylene derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
258066	H	F	Me	cyclopentylidene	C ₁₉ H ₁₉ FO ₂ S
258067	H	F	Me	2,4-cyclopentadien-1-ylidene	C ₁₉ H ₁₅ FO ₂ S
258068	F	Me	NH2	cyclopentylidene	C ₁₉ H ₂₀ FNO ₂ S

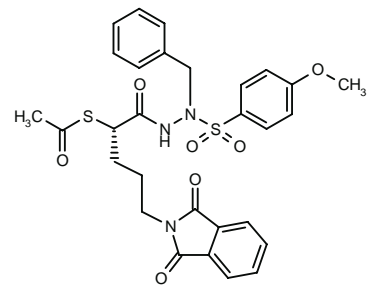
SOURCE – UPSA.

REFERENCES

1. Nicolai, E. et al. (Labs. UPSA) *Carbocyclic diarylmethylene derivs., processes for their preparation and their uses in therapeutics.* US 5686460.

257206

2(S)-(Acetylsulfanyl)-N²-benzyl-N²-(4-methoxyphenylsulfonyl)-5-phthalimidopentanohydrazide



C29-H29-N3-O7-S2; Mol wt: 595.68

2. Lell, B. et al. *A randomized, double-blind, placebo-controlled study to evaluate the suppressive prophylactic activity of atovaquone plus proguanil (Malarone™) in children at risk of developing Plasmodium falciparum infection.* Amer J Trop Med Hyg 1997, 57 (3, Suppl.): Abst 8.

3. Radloff, P.D. et al. *Atovaquone and proguanil for Plasmodium falciparum malaria.* Lancet 1996, 347: 1511.

4. Sabchareon, A. et al. *Uncontrolled clinical trial of a combination of atovaquone and proguanil in the treatment of acute P. falciparum malaria in children in Thailand.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst P-01-116.

5. Shanks, D. et al. *A randomized, double-blinded, placebo-controlled field trial of the chemosuppressive activity of atovaquone/proguanil (Malarone®) for P. falciparum in Kenya.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-84-2.

6. *Glaxo Wellcome development pipeline.* Prous Science Daily Essentials February 28, 1997.

7. *Malarone launch.* Glaxo Wellcome Company Communication 1997, October 14.

8. *New antimalarial combination launched this week in second market.* Prous Science Daily Essentials October 14, 1997.

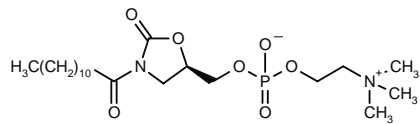
9. *U.K. launch for Malarone, a potent new antimalarial combination.* Prous Science Daily Essentials November 3, 1997.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

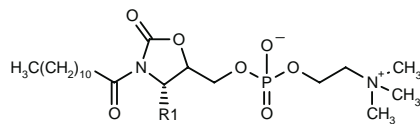
256450

Phosphocholine 3-(dodecanoyl)-2-oxooxazolidin-5(R)-yl-methyl monoester



C21-H41-N2-O7-P; Mol wt: 464.54

ACTION – Antiinflammatory and antiallergic agent, an inhibitor of phospholipase A₂ (PLA₂). Within this series of oxazolidinone derivatives, the following are also included:



Compound	R1	Isomer	Formula
258230	Pr	5S	C ₂₄ H ₄₇ N ₂ O ₇ P
258231	Pr	5R	C ₂₄ H ₄₇ N ₂ O ₇ P
258232	H	5S	C ₂₁ H ₄₁ N ₂ O ₇ P

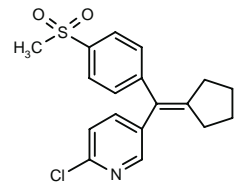
SOURCE – Santen.

REFERENCES

1. Katsumura, N. (Santen Pharm. Co., Ltd.) *Oxazolidinone derivs.* JP 97241278.

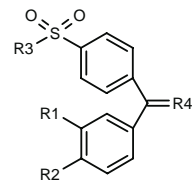
256659

2-Chloro-5-[1-cyclopentylidene-1-[4-(methylsulfonyl)-phenyl]methyl]pyridine



C18-H18-Cl-N-O2-S; Mol wt: 347.86

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; 65% inhibition at 10 μM vs. 0% inhibition of COX-1 at 10 μM using purified sheep enzymes). *In vivo* activity was demonstrated in rats in the carrageenan-induced paw edema test (45.8 ± 9.8% inhibition at 100 mg/kg p.o.) and in the kaolin-induced arthritis test (55.0 ± 15.7% inhibition at 100 mg/kg p.o.). A representative compound from a series of specifically claimed carbocyclic diaryl methylene derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
258066	H	F	Me	cyclopentylidene	C ₁₉ H ₁₉ FO ₂ S
258067	H	F	Me	2,4-cyclopentadien-1-ylidene	C ₁₉ H ₁₅ FO ₂ S
258068	F	Me	NH2	cyclopentylidene	C ₁₉ H ₂₀ FNO ₂ S

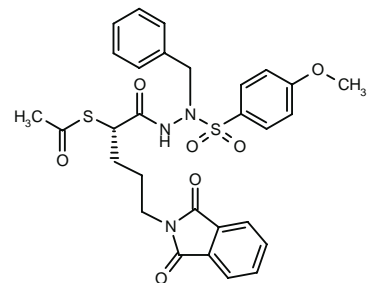
SOURCE – UPSA.

REFERENCES

1. Nicolai, E. et al. (Labs. UPSA) *Carbocyclic diarylmethylene derivs., processes for their preparation and their uses in therapeutics.* US 5686460.

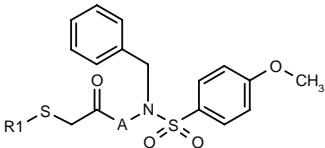
257206

2(S)-(Acetylsulfanyl)-N²-benzyl-N²-(4-methoxyphenylsulfonyl)-5-phthalimidopentanohydrazide



C29-H29-N3-O7-S2; Mol wt: 595.68

ACTION – An inhibitor of matrix metalloproteinases such as stromelysin, collagenase and gelatinase and of the release of tumor necrosis factor (TNF- α), potentially useful in the treatment of osteoarthritis and rheumatoid arthritis, as well as other inflammatory disorders and cancer. A representative compound from a series of specifically claimed peptidyl derivatives, wherein the following are also included:



Compound	R1	A	Formula
258259	Ac	-NH-	C ₁₈ H ₂₀ N ₂ O ₅ S ₂
258260	Ac	-CH(i-Bu)-	C ₂₃ H ₂₉ NO ₅ S ₂
258261	H	-NH-	C ₁₆ H ₁₈ N ₂ O ₄ S ₂

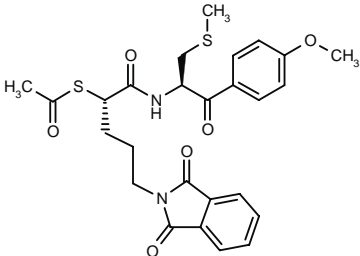
SOURCE – Chiroscience.

REFERENCES

1. Baxter, A.D. et al. (Chiroscience, Ltd.) *Peptidyl cpds. having MMP and TNF inhibitor activity*. WO 9737973.

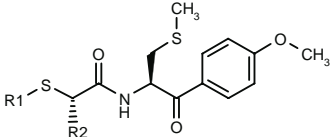
257207

2(S)-(Acetylsulfanyl)-N-[1(R)-(4-methoxybenzoyl)-2-(methylsulfanyl)ethyl]-5-phthalimidopentanamide

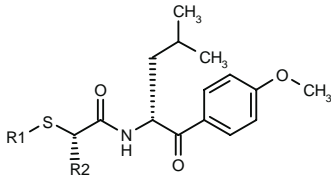


C26-H28-N2-O6-S2; Mol wt: 528.64

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as stromelysin, collagenase and gelatinase and of the production of tumor necrosis factor (TNF- α), with potential in the treatment of inflammation, autoimmune diseases, cardiovascular disorders, rheumatoid arthritis and tumors. Other specifically claimed peptidyl derivatives include the following:



Compound	R1	R2	Formula
258263	Ac	H	C ₁₅ H ₁₉ NO ₄ S ₂
258265	H	1,3-dioxo-2-isindolyl-(CH2)3	C ₂₄ H ₂₆ N ₂ O ₅ S ₂
258267	H	H	C ₁₃ H ₁₇ NO ₃ S ₂



Compound	R1	R2	Formula
258262	Ac	1,3-dioxo-2-isindolyl-(CH2)3	C ₂₈ H ₃₂ N ₂ O ₆ S
258264	Ac	H	C ₁₇ H ₂₃ NO ₄ S
258266	H	1,3-dioxo-2-isindolyl-(CH2)3	C ₂₆ H ₃₀ N ₂ O ₅ S
258268	H	H	C ₁₅ H ₂₁ NO ₃ S

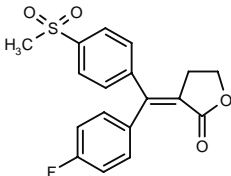
SOURCE – Chiroscience.

REFERENCES

1. Bacter, A.D. et al. (Chiroscience, Ltd.) *Peptidyl cpds. having MMP and TNF inhibitory activity*. WO 9737974.

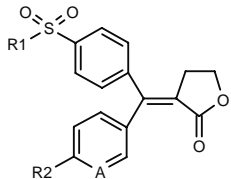
257212

(E)-3-[1-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylene]tetrahydrofuran-2-one



C18-H15-F-O4-S; Mol wt: 346.37

ACTION – Antiinflammatory and analgesic agent, a selective cyclooxygenase type 2 (COX-2) inhibitor with an IC₅₀ of 674 \pm 46 nM against COX-2 purified from sheep placenta and an IC₅₀ > 300,000 nM against COX-1 purified from sheep seminal vesicles (selectivity ratio > 445). It inhibited carrageenan-induced rat paw edema (ID₅₀ = 1.8 mg/kg p.o.) and exerted significant analgesic activity in the kaolin-induced rat arthritis model (ED₅₀ = 7.6 mg/kg p.o.), whereas it had very low ulcerogenic potential in rats (UD₅₀ > 1000 mg/kg p.o.; UD₅₀ indomethacin = 8.3 mg/kg p.o.). Other specifically claimed furan diarylmethylidene derivatives include the following:



Compound	R1	R2	A	Formula
258168	Me	Cl	CH	C ₁₈ H ₁₅ ClO ₄ S
258169	Me	Cl	C(Cl)	C ₁₈ H ₁₄ Cl ₂ O ₄ S
258170	Me	Cl	N	C ₁₇ H ₁₄ ClNO ₄ S
258171	NH2	Cl	CH	C ₁₇ H ₁₄ ClNO ₄ S
258172	NH2	Me	C(F)	C ₁₈ H ₁₆ FNO ₄ S

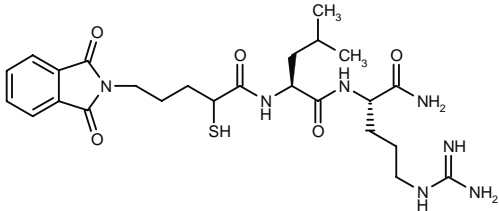
SOURCE – UPSA.

REFERENCES

1. Nicolai, E. and Teulon, J.-M. (Labs. UPSA) *Novel furan diarylmethylidene derivs., method for their preparation and therapeutical uses thereof.* FR 2747123, FR 2747124, WO 9737984.

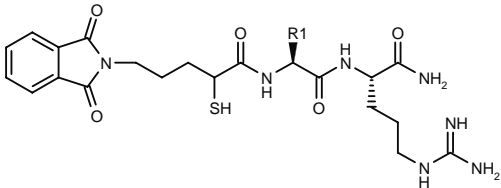
257223

2-Mercapto-5-phthalimidopentanoyl-L-leucyl-L-argininamide



C25-H37-N7-O5-S; Mol wt: 547.67

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as stromelysin, collagenase and gelatinase and of the release of tumor necrosis factor (TNF-α), with potential in the treatment of inflammation, autoimmune diseases, cardiovascular disorders, neurological disorders and tumors. Other specifically claimed mercaptoalkylpeptidyl compounds include the following:



Compound	R1	Formula
258555	(S)-CH(Me)Et	C ₂₅ H ₃₇ N ₇ O ₅ S
258556	Pr	C ₂₄ H ₃₅ N ₇ O ₅ S
258557	i-Pr	C ₂₄ H ₃₅ N ₇ O ₅ S

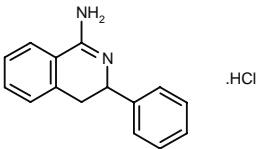
SOURCE – Chiroscience.

REFERENCES

1. Baxter, A.D. et al. (Chiroscience, Ltd.) *Peptidyl cpds. having MMP and TNF-liberation inhibitory activity.* WO 9738007.

257244

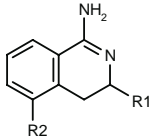
3-Phenyl-3,4-dihydroisoquinoline-1-amine hydrochloride



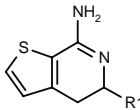
C15-H14-N2.HCl; Mol wt: 258.75

ACTION – Antiinflammatory agent thought to act by virtue of its ability to inhibit the inducible isoform of the enzyme nitric oxide synthase (iNOS) in macrophages (IC₅₀ < 25 μM in murine macrophage J774A-1 cells). The compound

may also inhibit the neuronal isoform (nNOS) and thus may also be useful for the treatment of neurodegenerative and CNS disorders. Within this series of specifically claimed aminoisoquinolines and aminothienopyridines, the following are also included:



Compound	R1	R2	Formula
258793	4-F-Ph	H	C ₁₅ H ₁₃ FN ₂
258794	2-furyl	H	C ₁₃ H ₁₂ N ₂ O
258795	cyclopropyl	H	C ₁₂ H ₁₄ N ₂
258796	4-F-Ph	F	C ₁₅ H ₁₂ F ₂ N ₂
258797	ethynyl	H	C ₁₁ H ₁₀ N ₂
258798	2-thiazolyl	H	C ₁₂ H ₁₁ N ₃ S



Compound	R1	Formula
258799	Ph	C ₁₃ H ₁₂ N ₂ S
258800	2-thienyl	C ₁₁ H ₁₀ N ₂ S ₂
258801	1-Me-2-pyrrolyl	C ₁₂ H ₁₃ N ₃ S
258802	2-thiazolyl	C ₁₀ H ₉ N ₃ S ₂
258803	cyclobutyl	C ₁₁ H ₁₄ N ₂ S

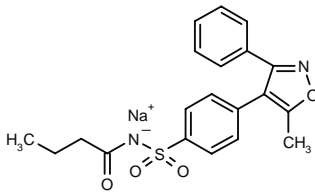
SOURCE – Astra.

REFERENCES

1. Hamley, P. et al. (Astra Pharm., Ltd.) *Aminoisoquinolines and aminothienopyridine derivs. and their use as antiinflammatory agents.* WO 9738977.

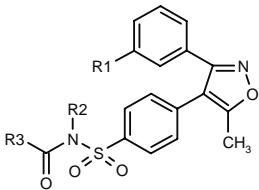
257249

N-[4-(5-Methyl-3-phenylisoxazol-4-yl)phenylsulfonyl]-butyramide sodium salt



C20-H19-N2-Na-O4-S; Mol wt: 406.43

ACTION – Antiinflammatory agent, a prodrug of a known selective cyclooxygenase type 2 (COX-2) inhibitor. Compound was shown to be completely converted to the active inhibitor when incubated with S9 liver fractions at 37 °C. *In vivo* activity was evaluated in the rat carrageenan-induced paw edema test (60% inhibition at 30 mg/kg p.o.) and in the rat carrageenan-induced hyperalgesia test (33% inhibition at 10 mg/kg p.o.). A representative compound from a series of *N*-substituted sulfonamide prodrugs of COX-2 inhibitors, wherein the following are also included:



Compound	R1	R2	R3	Formula
258757	F	H	Me	C ₁₈ H ₁₅ FN ₂ O ₄ S
258758	F	Na	Me	C ₁₈ H ₁₄ FN ₂ NaO ₄ S
258759	H	Na	Et	C ₁₉ H ₁₇ N ₂ NaO ₄ S

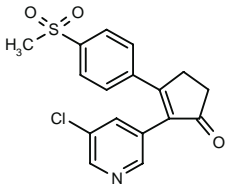
SOURCE – Searle.

REFERENCES

1. Talley, J.J. et al. (G.D. Searle & Co.) *Substd. benzenesulfonamide derivs. as pro-drugs of COX-2 inhibitors*. WO 9738986.

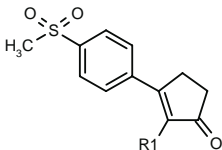
257715

2-(5-Chloro-3-pyridyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one



C17-H14-Cl-N-O3-S; Mol wt: 347.82

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2), as determined by measuring inhibition of lipopolysaccharide (LPS)-induced PGE₂ production in human whole blood (IC₅₀ = 0.58 μM); COX-1-inhibitory activity was evaluated in U937 cell microsomes specifically expressing the enzyme (IC₅₀ > 100 μM; selectivity ratio > 112). Other specifically claimed pyridinyl-2-cyclopenten-1-ones include the following:



Compound	R1	Formula
258598	3-Pyr	C ₁₇ H ₁₅ NO ₃ S
258599	5-Br-3-Pyr	C ₁₇ H ₁₄ BrNO ₃ S
259766	6-Me-3-Pyr	C ₁₈ H ₁₇ NO ₃ S
259767	6-MeO-3-Pyr	C ₁₈ H ₁₇ NO ₄ S
259768	2-Pyr	C ₁₇ H ₁₅ NO ₃ S
259769	5-Cl-2-Pyr	C ₁₇ H ₁₄ ClNO ₃ S
259770	5-Br-2-Pyr	C ₁₇ H ₁₄ BrNO ₃ S
259771	4-Pyr	C ₁₇ H ₁₅ NO ₃ S

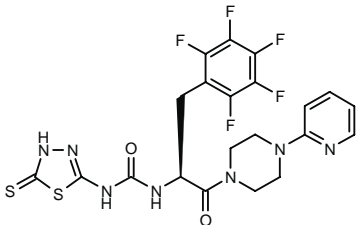
SOURCE – Merck Frosst.

REFERENCES

1. Black, C. et al. (Merck Frosst Canada, Inc.) *Pyridinyl-2-cyclopenten-1-ones as selective cyclooxygenase-2 inhibitors*. WO 9740012.

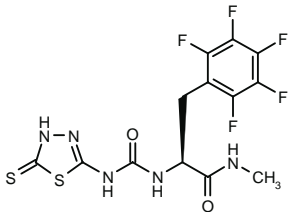
257723

N-[2-(Pentafluorophenyl)-1(S)-[4-(2-pyridyl)piperazin-1-ylcarbonyl]ethyl]-N'-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)urea



C21-H18-F5-N7-O2-S2; Mol wt: 559.53

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases, particularly stromelysin (K_i = 0.01 μM). Another representative and particularly preferred compound within this series of specifically claimed thiadiazolyl(thio)ureas is:



258597: C13-H10-F5-N5-O2-S2

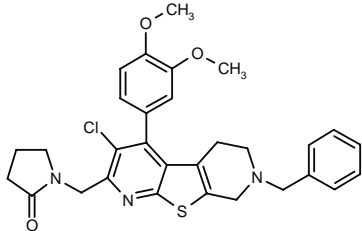
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Jacobsen, E.J. et al. (Pharmacia & Upjohn Co.) *Thiadiazolyl(thio)ureas useful as matrix metalloprotease inhibitors*. WO 9740031.

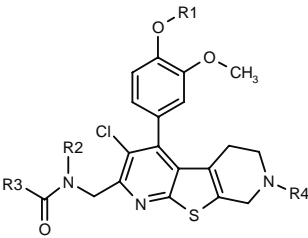
257739

1-[7-Benzyl-3-chloro-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridin-2-ylmethyl]pyrrolidin-2-one



C30-H30-Cl-N3-O3-S; Mol wt: 548.10

ACTION – Antiarthritic and antiinflammatory agent and bone resorption inhibitor, shown to produce 78% inhibition of paw swelling in a rat adjuvant arthritis model at 6.25 mg/kg/day p.o. x 14 days. Bone resorption-inhibitory activity was demonstrated in an *in vitro* rat model (47% inhibition at 10 μM, as determined by measuring the release of ⁴⁵Ca). Also claimed for the treatment of immune-related diseases by virtue of its ability to inhibit the production of cytokines such as interleukin-2 (IL-2) and interferon gamma. Other compounds from this series of specifically claimed thienopyridine derivatives include the following:



Compound	R1	R2,R3	R4	Formula
258840	Me	-(CH2)4-	CH2Ph	C ₃₁ H ₃₂ ClN ₃ O ₃ S
258841	Me	-(CH2)5-	CH2Ph	C ₃₂ H ₃₄ ClN ₃ O ₃ S
258842	H	-(CH2)3-	CH2Ph	C ₂₉ H ₂₈ ClN ₃ O ₃ S
258843	Me	-COCH2CH2-	CH2Ph	C ₃₀ H ₂₈ ClN ₃ O ₄ S
258844	Me	-(CH2)3-	H	C ₂₃ H ₂₄ ClN ₃ O ₃ S

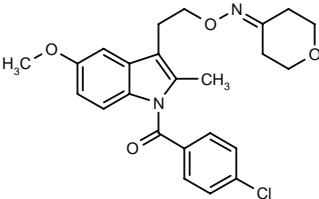
SOURCE – Takeda.

REFERENCES

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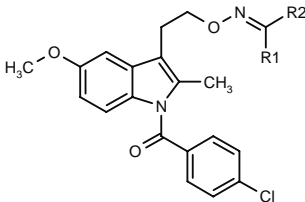
257759

Tetrahydropyran-4-one O-[2-[1-(4-chlorobenzyl)-5-methoxy-2-methylindol-3-yl]ethyl]oxime



C24-H25-Cl-N2-O4; Mol wt: 440.93

ACTION – Antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; 72% inhibition at 0.1 μM using human recombinant enzyme) as compared to COX-1 (0% inhibition at 1 μM using human recombinant enzyme). Other compounds from this series of specifically claimed iminoxy derivatives of substituted indoles and indenenes include the following:



Compound	R1	R2	Formula
259222	Me	CH=CHCO2H	C ₂₄ H ₂₃ ClN ₂ O ₅
259223	H	CH(OH)CH2OH	C ₂₂ H ₂₃ ClN ₂ O ₅

SOURCE – Abbott.

REFERENCES

1. Brooks, C.D.W. et al. (Abbott Labs.) *Iminoxy derivs. of indole and indene cpds. as inhibitors of prostaglandin biosynthesis.* WO 9741100.

DEXIBUPROFEN

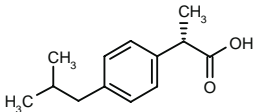
Rec INN

157701

(S)-α-Methyl-4-(2-methylpropyl)benzeneacetic acid

2(S)-(4-Isobutylphenyl)propionic acid

(S)-(+)-p-Isobutylhydratropic acid



C13-H18-O2; Mol wt: 206.28

ACTION – Nonsteroidal antiinflammatory agent with analgesic and antipyretic properties that acts by inhibiting cyclooxygenase.

INDICATION – Treatment of painful and inflammatory rheumatic disorders.

PRESENTATION – Tablets, 150 and 300 mg.

PROPRIETARY NAME – DexOptifen (CH).

SOURCE – Spig.

REFERENCES

1. Cremer, K. and Müller, W. *Capsule formulation with accelerated dissolution of S(+)-ibuprofen from complex with colestipol resin.* Pharm Res 1995, 12(9, Suppl.): Abst PT 6053.

2. Gabard, B. et al. *Comparison of the bioavailability of dexibuprofen administered alone or as part of racemic ibuprofen.* Eur J Clin Pharmacol 1995, 48(6): 505.

3. Lee, J. et al. *The effect of four common cellulosic excipients on the degradation of S(+)-ibuprofen into isobutylacetophenone.* Pharm Res 1995, 12(9, Suppl.): Abst PT 6135.

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7. Walser, S. et al. *Preliminary toxicokinetic study with different crystal forms of S(+)-ibuprofen (dexibuprofen) and R,S-ibuprofen in rats.* Arzneim-Forsch-Drug Res 1997, 47(6): 750.

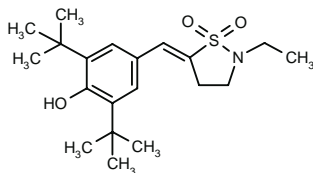
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9. Wang, B.C. et al. *The antinociceptive effect of S(+)-ibuprofen in rabbits: Epidural versus intravenous administration.* Anesth Analg 1995, 80(1): 92.

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11. *Dexibuprofen launch.* Spiring AG Company Communication 1997, December 2.

12. *New product intros.* Drug News Perspect 1997, 10(10): 621.

S-2474***210134***(E)*-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethylisothiazolidine 1,1-dioxide

C20-H31-N-O3-S; Mol wt: 365.53

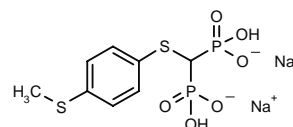
ACTION – Antiarthritic agent with a dual NSAID (non-steroidal antiinflammatory drug) and DMARD (disease-modifying antirheumatic drug) profile. *In vitro*, it potently inhibited cyclooxygenase type 2 (COX-2; IC₅₀ = 0.2-3.6 nM for inhibition of IL-1-stimulated PGE₂ production in various cell lines), osteoclast formation from IL-1-stimulated mouse bone marrow cells (IC₅₀ = 1.3 nM) and the production of inflammatory mediators such as LTB₄, IL-1, IL-6, IL-8 and nitric oxide (NO) from stimulated cell lines (IC₅₀ = 0.5-30 μM). The compound blocked the cytotoxic effect of activated murine macrophages and the mitogenic response of concanavalin A (ConA)- and lipopolysaccharide (LPS)-stimulated murine lymphocytes (IC₅₀ = 1.3-5.0 μM). *In vivo* in rats with adjuvant arthritis, the compound showed antiinflammatory (ED₅₀ = 0.88 mg/kg p.o.) and analgesic effects (minimum effective dose [MED] = 3 mg/kg p.o.) comparable to tenidap, and it was more effective than tenidap against joint destruction (MED = 1 mg/kg p.o.). In mice which spontaneously develop degenerative polyarthritis, the compound at doses of 10-50 mg/kg/day for 6-8 months produced radiological improvement comparable to ciclosporin and superior to tenidap and indomethacin. At doses up to 400 mg/kg in rats, the compound did not produce ulcerogenic effects.

SOURCE – Shionogi.**REFERENCES**

1. Haga, N. et al. (Shionogi & Co., Ltd.) *Method for producing benzylidene derivs.* EP 626377.
2. Hamada, Y. et al. (Shionogi & Co., Ltd.) *Preparation method of benzylidene derivs.* JP 96027134.
3. Hamada, Y. et al. (Shionogi & Co., Ltd.) *Method for selective isolation of crystals of benzylidene deriv.* JP 96217764.
4. Matsumoto, S. et al. (Shionogi & Co., Ltd.) *Benzylidene derivs.* EP 595546, JP 94211819, US 5418230.
5. Tsuru, T. and Matsumoto, S. (Shionogi & Co., Ltd.) *Preparation method of chloroalkyl-sulfonyl chlorides.* JP 95285926.
6. Inagaki, M. et al. *A novel antiarthritic agent S-2474: Synthesis and pharmacological effects.* 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-25.
7. Matsumoto, S. et al. *A novel antiarthritic agent S-2474 with dual profile on NSAID plus DMARD: In vitro characterizations.* Inflamm Res 1997, 46(Suppl. 3): Abst P-IV-6-03.
8. Jyoyama, H. et al. *A novel antiarthritic agent S-2474 with dual profile of NSAID plus DMARD: In vivo characterizations.* Inflamm Res 1997, 46(Suppl. 3): Abst P-IV-6-04.

*Identified compound **210134** Drug Data Rep 1994, 16(8): 700.**TRK-530****257456**

4-(Methylsulfanyl)phenylsulfanylmethanediphosphonic acid disodium salt

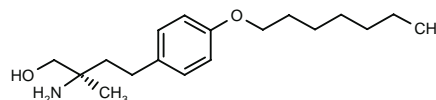


C8-H10-Na2-O6-P2-S2; Mol wt: 374.21

ACTION – Antiarthritic agent, a diphosphonate derivative shown to inhibit the histopathological and clinical progression of type II collagen-induced arthritis in mice, with activity at 50 mg/kg/day s.c. comparable to that of prednisolone (5 mg/kg/day s.c.) and indomethacin (2 mg/kg/day s.c.). It significantly inhibited the delayed-type hypersensitivity (DTH) response to type II collagen in arthritic mice at a dose of 50 mg/kg s.c. but did not suppress anti-type II collagen IgG antibody production; it also inhibited lipopolysaccharide (LPS) induced IL-1β production from J774.1 cells. TRK-530 thus appears to act via a mechanism different from that of prednisolone or indomethacin.

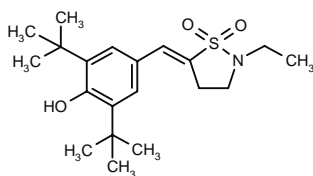
SOURCE – Toray.**REFERENCES**

1. Kawabe, N. et al. (Toray Ind., Inc.) *Methanediphosphonic acid deriv., production thereof and medicinal use thereof.* EP 594857, WO 9305052.
2. Takanishi, K. et al. (Toray Ind., Inc.) *Process for producing methanediphosphonate cpd.* WO 9419359.
3. Takaoka, Y. et al. *The effect of TRK-530 on experimental arthritis in mice.* Biol Pharm Bull 1997, 20(11): 1147.

IMMUNOLOGIC DRUGS**236135***(R)*-2-Amino-4-(4-heptyloxyphenyl)-2-methyl-1-butanol

C18-H31-N-O2; Mol wt: 293.45

ACTION – Immunosuppressive agent, a nonsymmetric analog of FTY-720. It was more active than ciclosporin and FTY-720 in a rat model of graft-versus-host reaction using a popliteal lymph node assay (ID₅₀ = 0.088 mg/kg p.o. vs. 2.8 and 0.2 mg/kg p.o., respectively, for ciclosporin and FTY-720), and in reducing T-cell number in peripheral blood (ID₅₀ = 0.0092 mg/kg p.o. vs. > 30 and 0.024 mg/kg p.o., respectively). Another 2,2-disubstituted 2-aminoethanol analog of FTY-720 is:

S-2474***210134***(E)*-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethylisothiazolidine 1,1-dioxide

C20-H31-N-O3-S; Mol wt: 365.53

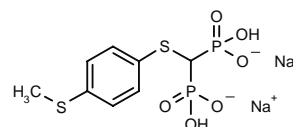
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*Identified compound **210134** Drug Data Rep 1994, 16(8): 700.**TRK-530****257456**

4-(Methylsulfanyl)phenylsulfanylmethanediphosphonic acid disodium salt

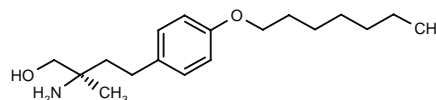


C8-H10-Na2-O6-P2-S2; Mol wt: 374.21

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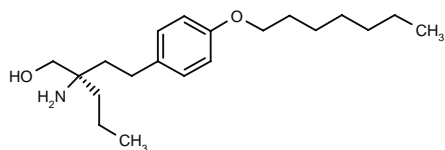
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2. Takanishi, K. et al. (Toray Ind., Inc.) *Process for producing methanediphosphonate cpd.* WO 9419359.
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C18-H31-N-O2; Mol wt: 293.45

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248483: C20-H35-N-O2

SOURCE – Yoshitomi.

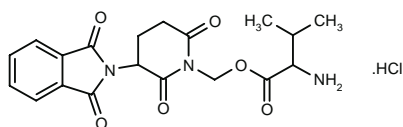
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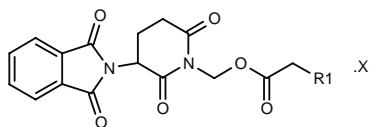
257216

2-Amino-3-methylbutyric acid 3-(1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidin-1-ylmethyl ester hydrochloride



C19-H21-N3-O6.HCl; Mol wt: 423.85

ACTION – Immunomodulating agent, a thalidomide pro-drug reported to be soluble in water at physiological pH and to be devoid of toxicity. *In vitro*, compound inhibited the lipopolysaccharide (LPS)-induced release of tumor necrosis factor- α (TNF- α) from human peripheral blood mononuclear cells with an IC_{50} value of 2.0 μ g/ml, and *in vivo* it produced 52% inhibition of the *Staphylococcus* enterotoxin B-induced increase in plasma IL-2 levels in galactosamine-treated mice at 400 mg/kg i.p. Other pro-drugs include the following:



Compound	R1	X	Formula
258571	t-BuOCONH		C ₂₁ H ₂₃ N ₃ O ₈
258572	NH ₂	HCl	C ₁₆ H ₁₅ N ₃ O ₆ .HCl
258573	NHMe	HCl	C ₁₇ H ₁₇ N ₃ O ₆ .HCl
258574	CH ₂ CO ₂ H		C ₁₈ H ₁₆ N ₂ O ₈

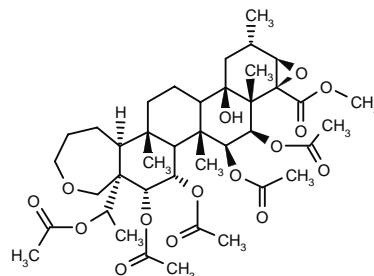
SOURCE – Grünenthal.

REFERENCES

1. Schneider, J. et al. (Grünenthal GmbH) *Acylated N-hydroxy methyl thalidomide pro-drugs with immunomodulator action*. WO 9737988.

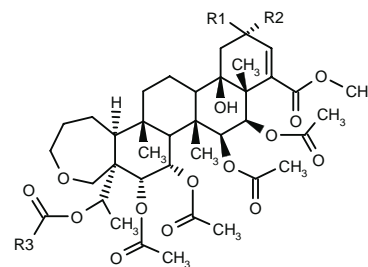
257619

[5a*R*-(5a α ,6 α ,7 α ,7b β ,8 β ,9 β ,9a β ,10 β ,11 β ,12 α ,13a β ,15a β ,15b α)]-6,7,9,10-Tetraacetoxy-5a-(1-acetoxyethyl)-10,11-epoxy-13a-hydroxy-7b,9a,12,15a-tetramethylperhydrochryseno[2,1-*c*]oxepin-10-carboxylic acid methyl ester



C40-H58-O15; Mol wt: 778.89

ACTION – Immunosuppressive agent for the treatment of autoimmune diseases and for the prevention of organ rejection that acts by inhibiting voltage-gated K_v1.3 potassium channels found in T-lymphocytes. A representative compound from a series of specifically claimed triterpene derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
258082	H	Me	Me	C ₄₀ H ₅₈ O ₁₄
258083	-O-		Me	C ₃₉ H ₅₂ O ₁₆
258084	H	Me	2-Br-Ph	C ₄₅ H ₅₇ BrO ₁₅

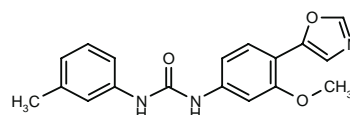
SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Triterpene derivs. with immunosuppressant activity*. US 5696156.

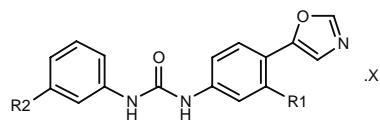
257721

N-[3-Methoxy-4-(5-oxazolyl)phenyl]-*N'*-(3-methylphenyl)-urea

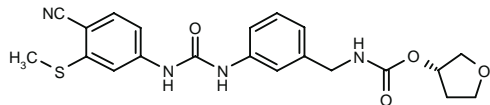


C18-H17-N3-O3; Mol wt: 323.35

ACTION – Immunosuppressant, an inhibitor of IMP (inosine monophosphate) dehydrogenase (IMPDH) also claimed for the treatment of cancer, vascular hyperproliferative disorders, inflammatory disorders, fungal and viral infections. Enzyme-inhibitory activity was assessed using human IMPDH type II (K_i < 50 nM). Within this series of urea derivatives, the following are also included:



Compound	R1	R2	X	Formula
258668	NH2	OMe		C ₁₇ H ₁₆ N ₄ O ₃
258669	N(Me)COCF3	Cl		C ₁₉ H ₁₄ ClF ₃ N ₄ O ₃
258670	N(Me)Ac	OMe		C ₂₀ H ₂₀ N ₄ O ₄
258671	NHCO2C(Me)3	OMe		C ₂₂ H ₂₄ N ₄ O ₅
258672	t-BuOCONHCH2	OMe		C ₂₃ H ₂₆ N ₄ O ₅
258673	CH2NHCO2Ph	OMe		C ₂₅ H ₂₂ N ₄ O ₅
258674	CH2NHCO2CH2Ph	OMe		C ₂₆ H ₂₄ N ₄ O ₅
258675	3-Pip-OCONHCH2	OMe	CF3CO2H	C ₂₄ H ₂₇ N ₅ O ₅ ·C ₂ H ₃ F ₃ O ₂



258676: C21-H22-N4-O4-S

SOURCE – Vertex.

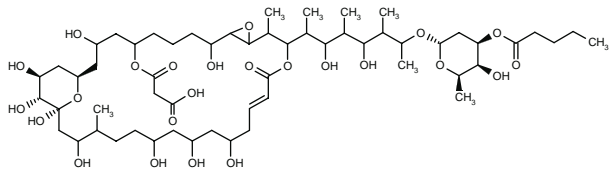
REFERENCES

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BRASILINOLIDE A

258352

(30*S*,31*R*,32*S*,34*R*)-Propanedioic acid mono[14-[6-[2,6-dideoxy-3-*O*-(1-oxopentyl)-β-*D*-lyxo-hexopyranosyloxy]-2,4-dihydroxy-1,3,5-trimethylheptyl]-3,9,20,22,24,28,30,31,32-nonahydroxy-13,27-dimethyl-16-oxo-11,15,34-trioxatricyclo[28.3.1.0^{10,12}]tetratriacont-17-en-5-yl]ester



C57-H98-O24; Mol wt: 1167.39

Colorless amorphous solid, [α]_D²⁸ –27.4° (c 1.0, MeOH).

ACTION – Immunosuppressive and antifungal agent, a 32-membered macrolide isolated from the culture broth of *Nocardia brasiliensis* IFM 0406. Compound showed potent immunosuppressive activity in the murine mixed lymphocyte reaction (MLR; IC₅₀ = 0.625 μg/ml) comparable to ciclosporin and ascomycin (IC₅₀ = 0.016 and 0.040 μg/ml, respectively) and no toxicity was observed in mice at 500 mg/kg i.v. (LD₅₀ = 107 and 25 mg/kg i.v. for ciclosporin and tacrolimus, respectively). As regards antimicrobial activity, it was only active against *Aspergillus niger* IFM 40406 (MIC = 3.13 μg/ml).

SOURCES – Chiba Univ., Chiba (JP); Hokkaido Univ., Sapporo (JP).

REFERENCES

1. Shigemori, H. et al. Brasilinolide A, new immunosuppressive macrolide from actinomycete *Nocardia brasiliensis*. Tetrahedron 1996, 52(27): 9031.

2. Tanaka, Y. et al. Brasilinolide A, a new macrolide antibiotic produced by *Nocardia brasiliensis*: Producing strain, isolation and biological activity. J Antibiot 1997, 50(12): 1036.

DACLIZUMAB

Prop INN; USAN

198590

Immunoglobulin G₁ (human–mouse monoclonal clone 1H4 γ-chain anti-human-interleukin-2 receptor), disulfide with human–mouse monoclonal clone 1H4 light chain, dimer

Genetically engineered human IgG₁ monoclonal antibody that binds specifically to the α-subunit (p55 α, CD25, or Tac subunit) of the human high-affinity IL-2 receptor, composed of human (90%) and murine (10%) antibody sequences; the human sequences are derived from the constant domains of human IgG₁ and the variable framework regions of the Eu myeloma antibody, and the murine sequences are derived from the complementarity-determining regions of a murine anti-Tac antibody

Dacliximab (former INN)

Ro-24-7375

SMART anti-Tac

ACTION – Immunosuppressive humanized anti-Tac monoclonal antibody (MAb) that binds specifically to the α-chain of the human high-affinity IL-2 receptor expressed on the surface of activated lymphocytes. The MAb inhibits IL-2 binding to its receptor, thereby inhibiting T-cell proliferation and activity against the donor organ.

INDICATION – Prevention of acute rejection episodes in kidney transplant recipients as part of an immunosuppressive regimen including ciclosporin and corticosteroids.

PRESENTATION – Single-use vials containing concentrate for further dilution, 25 mg daclizumab in 5 ml of solution (5 mg/ml).

PROPRIETARY NAME – Zenapax (US).

SOURCES – Protein Design Labs; marketed by Roche.

REFERENCES

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2. Anasetti, C. et al. A phase I/II randomized, double-blind, placebo-controlled multicenter trial of humanized anti-Tac for prevention of acute graft-versus-host disease (GVHD) in recipients of marrow transplants from unrelated donors. Blood 1995, 86(10, Suppl. 1): Abst 2472.

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10. Patel, I.H. et al. *The combination of Zenapax® and CellCept® as immunosuppression in renal transplantation does not adversely affect the pharmacokinetics of either agent*. 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 121.

11. Stock, P.G. et al. *In vivo (phase I) trial and in vitro efficacy of humanized anti-Tac for the prevention of rejection in renal transplant recipients*. Transplant Proc 1996, 28(2): 915.

12. Vincenti, F. *A phase III multi-center study of humanized anti-Tac (HAT) for the prevention of rejection in primary cadaveric renal allograft recipients*. 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 702.

13. Vincenti, F. et al. *Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation*. New Engl J Med 1998, 338(3): 161.

14. *Advisory panel to the FDA unanimously recommends PDL's Zenapax*. Prous Science Daily Essentials October 20, 1997.

15. *Anti-IL-2 for rejection*. Lancet 1997, 350(9088): 1376.

16. *Daclizumab launch*. Roche Company Communication 1998, February 5.

17. *First FDA approval for humanized MAb: Zenapax for renal transplant patients*. Prous Science Daily Essentials December 12, 1997.

18. *First launch for Zenapax*. Prous Science Daily Essentials February 17, 1998.

19. *Hoffmann-La Roche and Protein Design Labs announced that new phase III Zenapax® clinical results show six month improvement in mortality and graft survival*. Hoffmann-La Roche, Inc./Protein Design Labs, Inc. Press Release 1997, February 18.

20. *Protein Design Labs announces FDA approval of Roche's Zenapax: A breakthrough humanized monoclonal antibody*. Protein Design Labs, Inc. Press Release 1997, December 11.

21. *Protein Design Labs announces unanimous FDA advisory panel recommendation for approval of Zenapax®*. Protein Design Labs, Inc. Press Release 1997, October 17.

22. *Roche and Protein Design Labs report encouraging results from Zenapax trial*. Prous Science Daily Essentials May 20, 1997.

23. *Roche seeks European approval for humanized monoclonal antibody*. Prous Science Daily Essentials September 5, 1997.

24. *Roche seeks FDA approval for humanized antibody*. Prous Science Daily Essentials June 16, 1997.

25. *Zenapax® (daclizumab) sterile concentrate for injection*. Hoffmann-La Roche, Inc. Product Insert 1997, October.

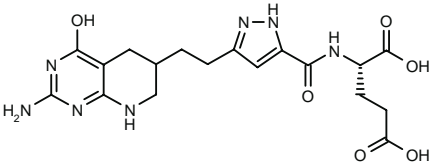
26. *Zenapax uveitis and transplant trial data reported*. Prous Science Daily Essentials February 19, 1998.

ONCOLYTIC DRUGS

ANTIMETABOLITES

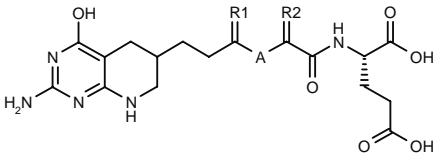
257765

N-[3-[2-(2-Amino-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-yl)ethyl]-1H-pyrazol-5-ylcarbonyl]-L-glutamic acid

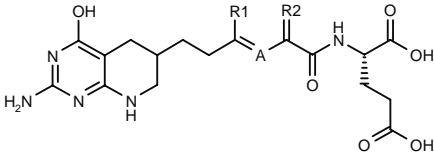


C18-H23-N7-O6; Mol wt: 433.42

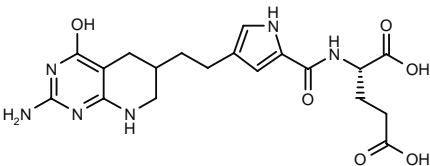
ACTION – Antineoplastic agent that acts by inhibiting enzymes that utilize folic acid, in particular metabolic derivatives of folic acid, as a substrate, such as glycylamide ribonucleotide formyltransferase, dihydrofolate reductase and thymidylate synthetase. *In vitro*, it inhibited the growth of lymphoblastic leukemia CCRF-CEM cells with an IC₅₀ value of 0.0019 µg/ml. Other compounds from this series of specifically claimed 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidines include the following:



Compound	R1	R2	A	Formula
259229	=CHCH=		NH	C ₁₉ H ₂₄ N ₆ O ₆
259233	=NCH=		S	C ₁₈ H ₂₂ N ₆ O ₆ S



Compound	R1	R2	A	Formula
259230	-NHCH=		CH	C ₁₉ H ₂₄ N ₆ O ₆
259232	-SCH=		N	C ₁₈ H ₂₂ N ₆ O ₆ S
259234	-NHCH=		N	C ₁₈ H ₂₃ N ₇ O ₆



259231: C19-H24-N6-O6

5. Mould, D.R. et al. *The pharmacokinetics (PK) of humanized anti-TAC (HAT) following single IV administration in graft-versus-host disease (GVHD) patients*. Pharm Res 1993, 10(10, Suppl.): Abst PPDM 8169.

6. Nashan, B. et al. *Reduction of acute cellular rejection by HAT (Zenapax®), kidney transplant patients*. 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 46.

7. Nashan, B. et al. *Results of a phase II clinical trial with daclizumab (Zenapax®) in liver transplanted patients*. 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 122.

8. Nieforth, K.A. et al. *Population pharmacokinetics of Zenapax in renal allograft recipients*. 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 359.

9. Nussenblatt, R.B. et al. *Strategies for the treatment of ocular disease*. 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 116.

10. Patel, I.H. et al. *The combination of Zenapax® and CellCept® as immunosuppression in renal transplantation does not adversely affect the pharmacokinetics of either agent*. 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 121.

11. Stock, P.G. et al. *In vivo (phase I) trial and in vitro efficacy of humanized anti-Tac for the prevention of rejection in renal transplant recipients*. Transplant Proc 1996, 28(2): 915.

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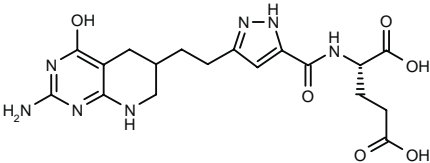
26. *Zenapax uveitis and transplant trial data reported*. Prous Science Daily Essentials February 19, 1998.

ONCOLYTIC DRUGS

ANTIMETABOLITES

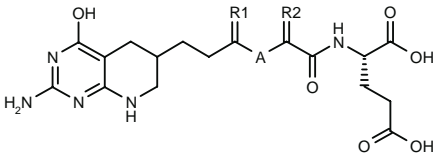
257765

N-[3-[2-(2-Amino-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-yl)ethyl]-1H-pyrazol-5-ylcarbonyl]-L-glutamic acid

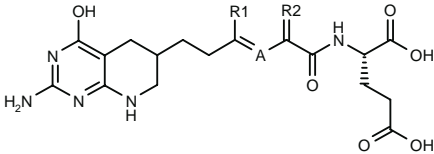


C18-H23-N7-O6; Mol wt: 433.42

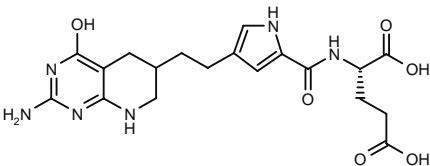
ACTION – Antineoplastic agent that acts by inhibiting enzymes that utilize folic acid, in particular metabolic derivatives of folic acid, as a substrate, such as glycylamide ribonucleotide formyltransferase, dihydrofolate reductase and thymidylate synthetase. *In vitro*, it inhibited the growth of lymphoblastic leukemia CCRF-CEM cells with an IC₅₀ value of 0.0019 µg/ml. Other compounds from this series of specifically claimed 5,6,7,8-tetrahydropyrido[2,3-d]pyrimidines include the following:



Compound	R1	R2	A	Formula
259229	=CHCH=		NH	C ₁₉ H ₂₄ N ₆ O ₆
259233	=NCH=		S	C ₁₈ H ₂₂ N ₆ O ₆ S



Compound	R1	R2	A	Formula
259230	-NHCH=		CH	C ₁₉ H ₂₄ N ₆ O ₆
259232	-SCH=		N	C ₁₈ H ₂₂ N ₆ O ₆ S
259234	-NHCH=		N	C ₁₈ H ₂₃ N ₇ O ₆



259231: C19-H24-N6-O6

SOURCES – Lilly; Princeton Univ., Princeton, NJ (US).

REFERENCES

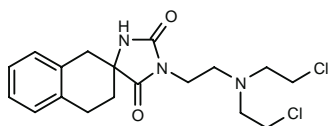
1. Taylor, E.C. et al. (Trustees Princeton Univ.; Eli Lilly & Co.) 5,6,7,8-Tetrahydropyrido[2,3-*d*]pyrimidines. WO 9741115.

DNA-DAMAGING DRUGS

β-TETHYMUSTINE

258131

1-[2-[Bis(2-chloroethyl)amino]ethyl]-3',4'-dihydrospiro[imidazolidine-4,2'(1'*H*)-naphthalene]-2,5-dione



C18-H23-Cl2-N3-O2; Mol wt: 384.30

White solid, *m.p.* 118 °C.

ACTION – Antineoplastic agent with alkylating activity comparable to spiromustine. Significant *in vivo* activity was observed in mice with i.p. Ehrlich ascites carcinoma (ILS = 80% at 6.0 mg/kg/day i.p. x 7; 2 of 6 mice alive at 90 days), sarcoma 180 (ILS = 224% at 8.0 mg/kg/day i.p. x 7; 3 of 6 mice alive at 90 days) and Dalton's lymphoma (ILS = 240% at 4.0 mg/kg/day i.p. x 7; 3 of 6 mice alive at 90 days); it was much more active than cyclophosphamide and had activity comparable to 5-fluorouracil. Compound exhibited relatively low toxicity in mice (LD₅₀ = 100.0 mg/kg i.p.; LD₁₀₀ = 150 mg/kg i.p.) and was more active when administered as divided doses than as a single dose.

SOURCE – Chittaranjan Natl. Cancer Inst., Calcutta (IN).

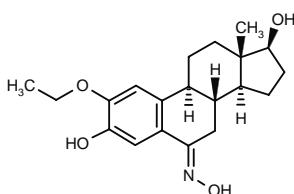
REFERENCES

1. Ghosh, M. et al. Evaluation of β-tethymustine, a new anticancer compound, in murine tumour models. Cancer Lett 1997, 119(1): 7.

ANTIMITOTIC DRUGS

253755

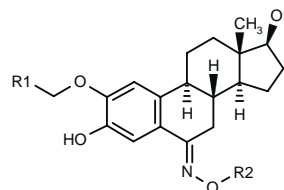
2-Ethoxy-3,17β-dihydroxyestra-1,3,5(10)-trien-6-one oxime



C20-H27-N-O4; Mol wt: 345.44

M.p. 228-30 °C.

ACTION – Antineoplastic agent, an analog of 2-methoxyestradiol (2-MeO-E), a natural mammalian tubulin polymerization inhibitor. Compound was more potent than 2-MeO-E and 2-ethoxyestradiol (2-EtO-E) in inhibiting both the polymerization of purified bovine brain tubulin (IC₅₀ = 1.1 ± 0.02 μM vs. 3.1 ± 0.05 and 1.3 ± 0.2 μM, respectively) and the binding of [³H]-colchicine to tubulin (63 ± 4% inhibition at 50 μM vs. 19 ± 3 and 51 ± 6% for 2-MeO-E and 2-EtO-E, respectively, at the same concentration). It was tested for antiproliferative activity against human lung HOP-62, colon HCT-116, CNS SF-539, melanoma UACC-62, ovarian OVCAR-3, renal SN12C, prostate DU-145 and breast MDA-MB-435 cancer cell lines in the NCI screen, giving GI₅₀ values of 0.011, 0.011, 0.013, 0.017, 0.017, 0.021, 0.026 and 0.010 μM, respectively. It had no significant affinity for the estrogen receptor in a rat uterine cytosol assay (relative binding affinity [RBA] < 0.001; RBA = 100 for estradiol and RBA = 0.245 and 0.011 for 2-MeO-E and 2-EtO-E, respectively). Compound is currently being studied *in vivo* for antitumor activity. Other related compounds with a similar activity profile are:



Compound	R1	R2	Formula
253756	CF ₃	H	C ₂₀ H ₂₄ F ₃ NO ₄
253757	Me	Me	C ₂₁ H ₂₉ NO ₄

SOURCES – Univ. Illinois, Urbana, IL (US); Natl. Cancer Inst., Frederick, MD (US); Pharm-Eco Labs; Purdue Univ., West Lafayette, IN (US).

REFERENCES

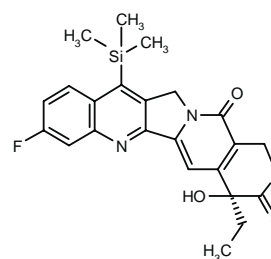
1. Cushman, M. et al. Synthesis of analogs of 2-methoxyestradiol with enhanced inhibitory effects on tubulin polymerization and cancer cell growth. J Med Chem 1997, 40(15): 2323.

DNA-INTERCALATING DRUGS

258687

4(*S*)-Ethyl-8-fluoro-4-hydroxy-11-(1,1,1-trimethylsilyl)-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione

11-Fluoro-7-(1,1,1-trimethylsilyl)-20(*S*)-camptothecin



C23-H23-F-N2-O4-Si; Mol wt: 438.53

ACTION – Antineoplastic agent, a camptothecin derivative with more potent antitumor activity than the parent compound *in vitro* against human promyelocytic leukemia HL-60, human teratocarcinoma 833K and hamster lung DC-3F tumor cell growth (IC_{50} = 0.75, 0.92 and 2.0 nM, respectively, vs. 5, 10 and 6-9 nM, respectively, for camptothecin). Compound was also more potent than camptothecin in enhancing the topoisomerase I-mediated cleavage of PBR₃₂₂ DNA (0.1-1 μ M vs. 1-2 μ M) and in inhibiting the topoisomerase I-mediated relaxation of PBR₃₂₂ DNA (< 0.1 μ M vs. 1-2 μ M). *In vivo* in mice bearing Lewis lung carcinoma, the compound (0.25 mg/kg i.p. b.i.d. x 5 days) induced a 56% reduction in tumor volume, while camptothecin produced a 44% reduction at 4-fold higher doses.

SOURCES – Memorial Sloan-Kettering Cancer Center, New York, NY (US); Univ. Pittsburgh, Pittsburgh, PA (US).

REFERENCES

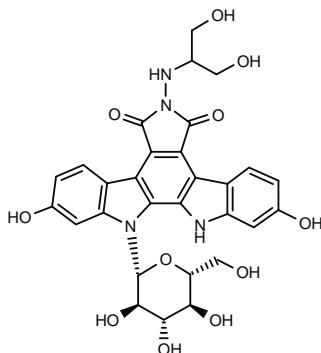
1. Josein, H. et al. 7-Silylcampthothecins (silatecans): A new family of camptothecin antitumor agents. *Bioorg Med Chem Lett* 1997, 7(24): 3189.

J-107088*

231292

12-(β -D-Glucopyranosyl)-2,10-dihydroxy-6-[2-hydroxy-1-(hydroxymethyl)ethylamino]-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione

ED-749



C29-H28-N4-O11; Mol wt: 608.56

ACTION – Antineoplastic agent, a topoisomerase I inhibitor (EC_{50} = 0.051 μ M) derived from J-107185 (NB-506⁺). The compound was shown to potently inhibit the proliferation of several tumor cells including P388 leukemia, human gastric cancer MKN-45 and human colon cancer DLD-1 cells (IC_{50} = 0.0015, 0.0048 and 0.120 μ M, respectively). *In vivo* in mice, it inhibited the growth of a wide spectrum of human tumor xenografts such as gastric cancer MKN-45, colon cancer LS180, breast cancer MX-1, lung cancer PC-13, prostate cancer PC-3, lung cancer LX-1 and uterine cancer HeLaS3 by 85-99% at doses of 80-500 mg/m² i.v. Clinical trials on J-107088 were scheduled to begin at the end of 1997.

SOURCE – Banyu.

REFERENCES

1. Kojiri, K. et al. (Banyu Pharm. Co., Ltd.) *Antitumor indolopyrrolocarbazole deriv.* EP 760375, WO 9530682.
2. Nishimura, T. et al. *Synthesis of indolocarbazole antitumor agents with a new glycosylation reaction.* 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-16.

3. Ohkubo, M. et al. *Structure-activity relationships of new indolocarbazole antitumor agents.* 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 2-P-15.

4. *Anticancer agent from Banyu heading for clinic.* Prous Science Daily Essentials March 14, 1997.

5. *Banyu developing anticancer agent in USA and Japan simultaneously.* Nikkei Sangyo Shinbun 1997, January 17.

6. *Banyu to shift development from NB-506 to new indolocarbazole.* Prous Science Daily Essentials June 13, 1997.

*Identified compound **231292** Drug Data Rep 1996, 18(7): 652.

*Drug Data Rep 1995, 17(8): 762.

HORMONAL AGENTS

256837

CysteinyI-prolyl-prolyl-prolyl-prolyl-seryl-seryl-glutamyl-histidyl-tryptophyl-seryl-tyrosyl-glycyl-leucyl-arginyl-prolyl-glycinamide

C84-H121-N25-O22-S; Mol wt: 1865.09

ACTION – Agent for the treatment of gonadotropin- and gonadal steroid hormone-dependent diseases such as breast cancer, uterine cancer, prostate cancer and benign prostatic hypertrophy, as well as for use in immunological contraception, an anti-gonadotropin-releasing hormone (anti-GnRH) immunogenic peptide conjugated to an immunological carrier such as diphtheria or tetanus toxoid, shown to induce effective levels of anti-GnRH antibodies following a single administration in rabbits and mice.

SOURCE – Aphton.

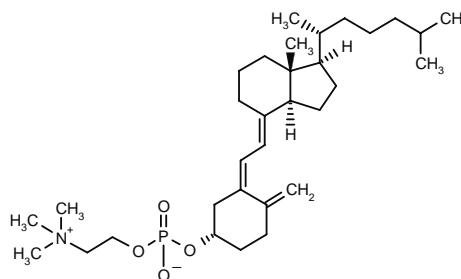
REFERENCES

1. Grimes, S. and Scibienski, R. (Aphton Corp.) *Immunogens against gonadotropin releasing hormone.* US 5688506.

CPR-2005

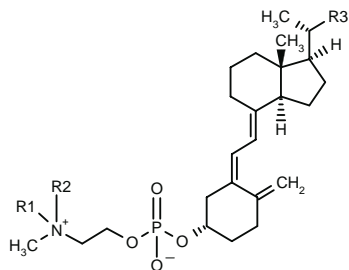
257265

Phosphocholine 9,10-secocholesta-5(Z),7(E),10(19)-trien-3 β -yl monoester

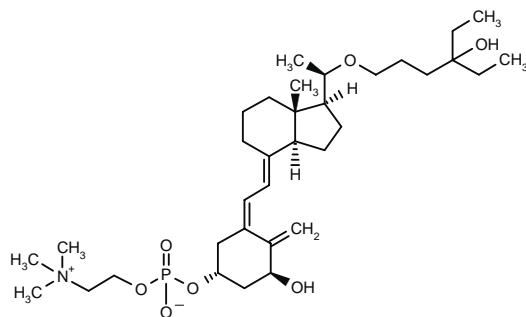


C32-H56-N-O4-P; Mol wt: 549.77

ACTION – Agent for the treatment of diseases associated with vitamin D deficiency, as well as for the treatment of tumors, inflammation and hyperproliferative skin diseases such as psoriasis, a phosphoethanolamine conjugate of vitamin D₃. Compound exhibited marked inhibition of human breast carcinoma MDA-MB-231 and human colon carcinoma HT-29 cell growth at 100 and 30 μM, respectively. Antihyperproliferative activity was demonstrated by marked inhibition of PAM-212 mouse keratinocytes at concentrations above 30 μM. Antiinflammatory activity was demonstrated *in vitro* by 90% inhibition of phorbol myristyl acetate (PMA)-induced activation of murine macrophages at 3 μM, being more potent than vitamin D₃ (9% inhibition at the same concentration), and *in vivo* by inhibition of the proliferation of PMA-induced mouse ear edema following topical application of a 5% solution. Other specifically claimed conjugates include the following:



Compound	R1	R2	R3	Formula
258201	Me	Me	(CH2)3C(Me)2OH	C ₃₂ H ₅₆ NO ₅ P
258202	Me	Me	(E)-(R)-i-PrCH(Me)CH=CH	C ₃₃ H ₅₆ NO ₄ P
258204	H	H	i-BuCH2CH2	C ₃₀ H ₅₂ NO ₄ P
258205	H	Me	i-BuCH2CH2	C ₃₁ H ₅₄ NO ₄ P



258203: C34-H60-N-O7-P

SOURCE – Clarion.

REFERENCES

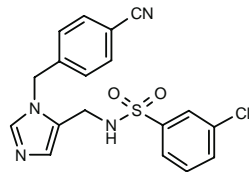
1. Peterson, A.C. and Yazdi, P.T. (Clarion Pharm., Inc.) *Phosphoethanolamine conjugates of vitamin D cpds.* US 5691328.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

257136

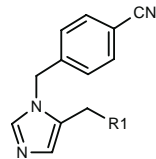
4-[5-(3-Chlorophenylsulfonamidomethyl)imidazol-1-ylmethyl]benzonitrile

3-Chloro-*N*-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]benzenesulfonamide



C18-H15-Cl-N4-O2-S; Mol wt: 386.86

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds include the following:



Compound	R1	Formula
257588	3-Cl-PhNHSO2	C ₁₈ H ₁₅ ClN ₄ O ₂ S
257589	NHSO2Ph	C ₁₈ H ₁₆ N ₄ O ₂ S
257590	SO2NHPh	C ₁₈ H ₁₆ N ₄ O ₂ S
257591	3-Cl-PhCH2SO2N(Me)	C ₂₀ H ₁₉ ClN ₄ O ₂ S
257592	3-Cl-PhCH2NHSO2	C ₁₉ H ₁₇ ClN ₄ O ₂ S
257593	3-Cl-PhSO2N(Me)	C ₁₉ H ₁₇ ClN ₄ O ₂ S
257594	3-Cl-PhN(Me)SO2	C ₁₉ H ₁₇ ClN ₄ O ₂ S
257595	N(Me)SO2Ph	C ₁₉ H ₁₈ N ₄ O ₂ S

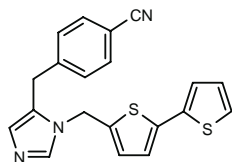
SOURCE – Merck & Co.

REFERENCES

1. Bergman, J. and Dinsmore, C. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase.* WO 9736583.

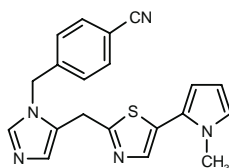
257138

4-[1-[5-(2-Thienyl)thien-2-ylmethyl]imidazol-5-ylmethyl]benzonitrile



C20-H15-N3-S2; Mol wt: 361.48

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase. Another specifically claimed biheteroaryl-containing compound is:

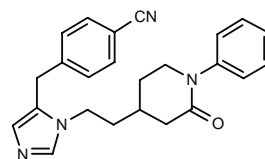


257597: C20-H17-N5-S

SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736585.



257586: C24-H24-N4-O

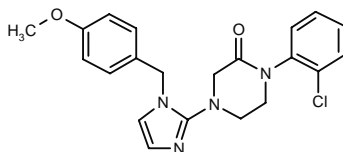
SOURCE – Merck & Co.

REFERENCES

1. Graham, S.L. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736605.

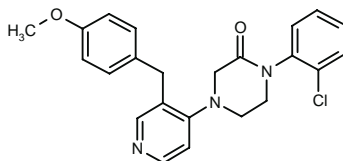
257141

1-(2-Chlorophenyl)-4-[1-(4-methoxybenzyl)imidazol-2-yl]piperazin-2-one



C21-H21-Cl-N4-O2; Mol wt: 396.88

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Another specifically claimed peptidomimetic piperazine-containing compound is:



257587: C23-H22-Cl-N3-O2

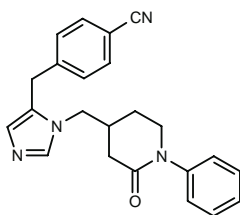
SOURCE – Merck & Co.

REFERENCES

1. Graham, S.L. and Williams, T.M. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736592.

257144

4-[1-(2-Oxo-1-phenylpiperidin-4-ylmethyl)imidazol-5-ylmethyl]benzonitrile

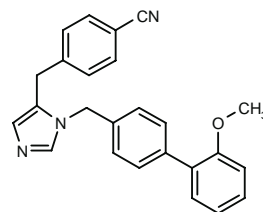


C23-H22-N4-O; Mol wt: 370.45

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Another representative compound within this series of specifically claimed peptidomimetic piperidinone derivatives is:

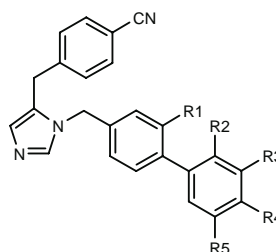
257160

4-[1-(2'-Methoxybiphenyl-4-ylmethyl)imidazol-5-ylmethyl]benzonitrile

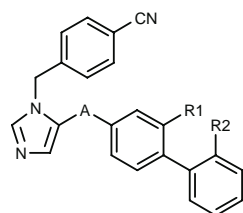


C25-H21-N3-O; Mol wt: 379.46

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced systemic toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Other specifically claimed biaryl-containing compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
258549	H	Me	H	H	H	C ₂₅ H ₂₁ N ₃
258550	H	H	Cl	H	Cl	C ₂₄ H ₁₇ Cl ₂ N ₃
258551	H	H	H	Cl	H	C ₂₄ H ₁₈ ClN ₃
258552	Me	H	OMe	H	H	C ₂₆ H ₂₃ N ₃ O
258577	H	Cl	H	H	Cl	C ₂₄ H ₁₇ Cl ₂ N ₃



Compound	R1	R2	A	Formula
258553	H	Me	O	C ₂₄ H ₁₉ N ₃ O
258554	F	H	-CH(OH)-	C ₂₄ H ₁₈ FN ₃ O

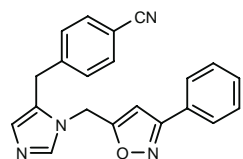
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736875.

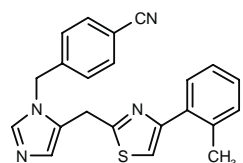
257164

4-[1-(3-Phenylisoxazol-5-ylmethyl)imidazol-5-ylmethyl]-benzonitrile

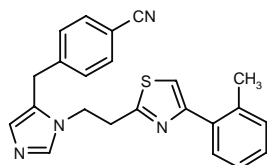


C21-H16-N4-O; Mol wt: 340.38

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Also claimed for the prevention of restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Within this series of specifically claimed arylheteroaryl-containing compounds, the following are also included:



258118: C22-H18-N4-S



258119: C23-H20-N4-S

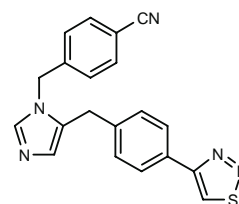
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736881.

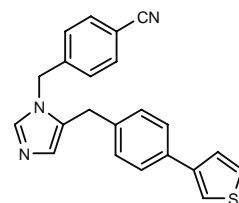
257167

4-[5-[4-(1,2,3-Thiadiazol-4-yl)benzyl]imidazol-1-yl-methyl]benzonitrile



C20-H15-N5-S; Mol wt: 357.43

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Also claimed for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Another specifically claimed peptidomimetic arylheteroaryl-containing compound is:



258117: C22-H17-N3-S

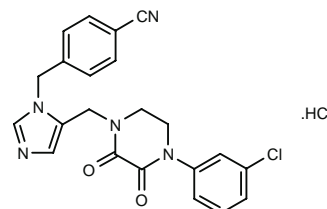
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736886.

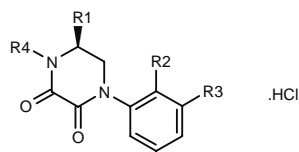
257170

4-[5-[4-(3-Chlorophenyl)-2,3-dioxopiperazin-1-ylmethyl]imidazol-1-ylmethyl]benzonitrile hydrochloride



C22-H18-Cl-N5-O2.HCl; Mol wt: 456.33

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed peptidomimetic 2,3-diketopiperazine-containing compounds include the following:



Compound	R1	R2	R3	R4	Formula
257916	i-Bu	H	OCF3	1-(4-CN-PhCH2)-2-Me-5-imidazolyl-CH2	C ₂₈ H ₂₈ F ₃ N ₅ O ₃ .HCl
257917	H	Me	Me	5-imidazolyl	C ₁₅ H ₁₆ N ₄ O ₂ .HCl

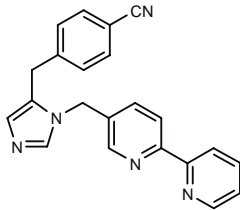
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. and Williams, T.M. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736889.

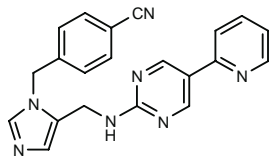
257171

4-[1-[6-(2-Pyridyl)pyridin-3-ylmethyl]imidazol-5-ylmethyl]-benzonitrile



C22-H17-N5; Mol wt: 351.41

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Another specifically claimed peptidomimetic biheteroaryl-containing compound is:



258116: C21-H17-N7

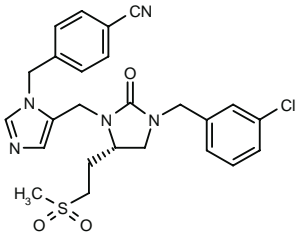
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736890.

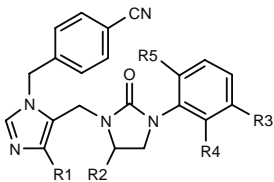
257173

4-[5-[3-(3-Chlorobenzyl)-5(S)-[2-(methylsulfonyl)ethyl]-2-oxoimidazolidin-1-ylmethyl]imidazol-1-ylmethyl]benzonitrile



C25-H26-Cl-N5-O3-S; Mol wt: 512.03

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of Ras farnesylation. Other specifically claimed imidazolidinone-containing compounds include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
258329	H	2-butynyl	Cl	H	H		C ₂₈ H ₂₂ ClN ₅ O
258333	H	Bu	Me	Me	H	S	C ₂₇ H ₃₁ N ₅ O
258334	H	H	Cl	H	H		C ₂₁ H ₁₈ ClN ₅ O
258335	Cl	Bu	Me	Me	Cl	S	C ₂₇ H ₂₉ Cl ₂ N ₅ O

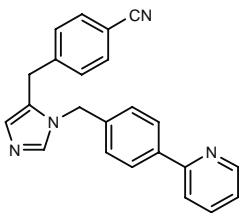
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. and Williams, T.M. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736892.

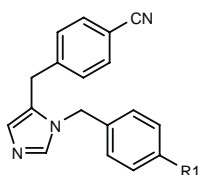
257175

4-[1-[4-(2-Pyridyl)benzyl]imidazol-5-ylmethyl]benzonitrile



C23-H18-N4; Mol wt: 350.42

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced systemic toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Other specifically claimed arylheteroaryl-containing compounds include the following:



Compound	R1	Formula
258547	3-Me-2-pyrazinyl	C ₂₃ H ₁₉ N ₅
258548	5-pyrimidinyl	C ₂₂ H ₁₇ N ₅

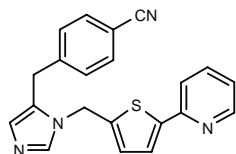
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736896.

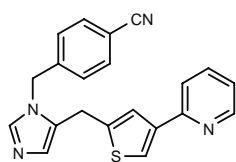
257176

4-[1-[5-(2-Pyridyl)thien-2-ylmethylimidazol-5-ylmethyl]-benzonitrile



C21-H16-N4-S; Mol wt: 356.44

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced systemic toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Another specifically claimed biheteroaryl-containing compound is:



258546: C21-H16-N4-S

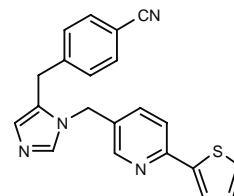
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736897.

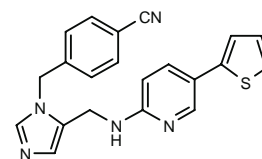
257177

4-[1-[6-(2-Thienyl)pyridin-3-ylmethyl]imidazol-5-ylmethyl]-benzonitrile



C21-H16-N4-S; Mol wt: 356.44

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced systemic toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Another specifically claimed biheteroaryl-containing compound is:



258545: C21-H17-N5-S

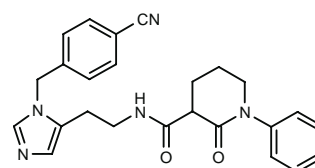
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736898.

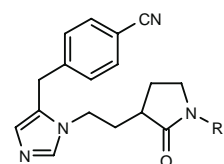
257179

4-[5-[2-(2-Oxo-1-phenylpiperidin-3-ylcarboxamido)ethyl]-imidazol-1-ylmethyl]benzonitrile



C25-H25-N5-O2; Mol wt: 427.50

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Also claimed for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Other specifically claimed peptidomimetic piperazine-containing compounds are:



Compound	R1	Formula
258154	Ph	C ₂₃ H ₂₂ N ₄ O
258155	CH2Ph	C ₂₄ H ₂₄ N ₄ O

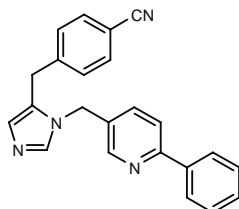
SOURCE – Merck & Co.

REFERENCES

1. Dinsmore, C.J. and Williams, T.M. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736900.

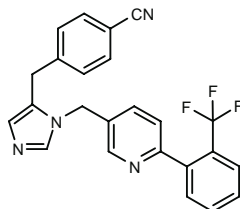
257180

4-[1-(6-Phenylpyridin-3-ylmethyl)imidazol-5-ylmethyl]-benzonitrile



C23-H18-N4; Mol wt: 350.42

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras, expected to possess improved pharmacokinetics and reduced systemic toxicity due to its lack of a thiol moiety. Also useful for preventing restenosis and for the treatment of benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections and polycystic kidney disease. Another specifically claimed arylheteroaryl-containing compound is:



258544: C24-H17-F3-N4

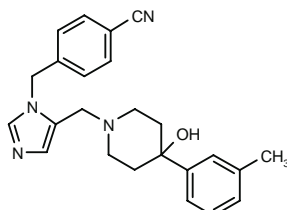
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9736901.

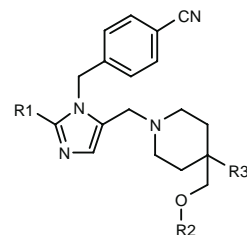
257230

4-[5-[4-Hydroxy-4-(3-methylphenyl)piperidin-1-ylmethyl]-imidazol-1-ylmethyl]benzonitrile

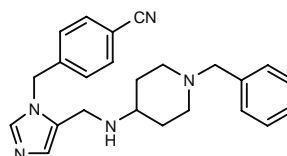


C24-H26-N4-O; Mol wt: 386.50

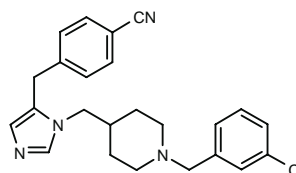
ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of Ras farnesylation. Within this series of specifically claimed piperidine-containing compounds, the following are also included:



Compound	R1	R2	R3	Formula
258322	H	H	3-CF3O-PhCH2	C ₂₆ H ₂₇ F ₃ N ₄ O ₂
258323	Me	H	4-Cl-2-Pyr-CH2	C ₂₅ H ₂₆ ClN ₅ O
258324	H	Me	3-Me-PhS	C ₂₆ H ₃₀ N ₄ OS
258325	H	H	3-Me-PhNH	C ₂₅ H ₂₉ N ₅ O
258326	H	CONH2	3-Me-PhNH	C ₂₆ H ₃₀ N ₆ O ₂



258327: C24-H27-N5



258328: C24-H25-Cl-N4

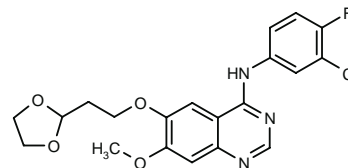
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9738665.

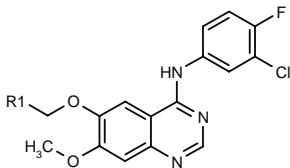
257255

4-(3-Chloro-4-fluorophenylamino)-6-[2-(1,3-dioxolan-2-yl)ethoxy]-7-methoxyquinazoline



C20-H19-Cl-F-N3-O4; Mol wt: 419.84

ACTION – Antiproliferative agent, an inhibitor of epidermal growth factor (EGF) tyrosine kinase ($IC_{50} = 0.01 \mu M$ using partially purified enzyme from human vulval carcinoma A-431 cells). *In vitro*, it inhibited EGF-stimulated growth of human nasopharyngeal cancer KB cells ($IC_{50} = 0.33 \mu M$), and *in vivo* it inhibited the growth of A-431 xenografts in nude mice with an ED_{50} value of approximately 50 mg/kg p.o. Other compounds from this series of specifically claimed quinazoline derivatives include the following:



Compound	R1	Formula
258826	1,3-dioxolan-2-yl	C ₁₉ H ₁₇ ClFN ₃ O ₄
258827	1,3-dioxolan-2-yl-CH ₂ CH ₂	C ₂₁ H ₂₁ ClFN ₃ O ₄
258828	1,3-dioxolan-4-yl	C ₁₉ H ₁₇ ClFN ₃ O ₄
258829	(R)-2,2-(Me)2-1,3-dioxolan-4-yl	C ₂₁ H ₂₁ ClFN ₃ O ₄
258830	(S)-2,2-(Me)2-1,3-dioxolan-4-yl	C ₂₁ H ₂₁ ClFN ₃ O ₄
258831	1,3-dioxan-2-yl-CH ₂	C ₂₁ H ₂₁ ClFN ₃ O ₄
258832	5-Me-1,3-dioxan-5-yl	C ₂₁ H ₂₁ ClFN ₃ O ₄
258833	3-Me-3-oxetanyl	C ₂₀ H ₁₉ ClFN ₃ O ₃

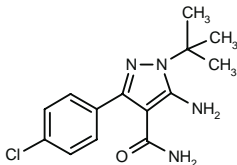
SOURCE – Zeneca.

REFERENCES

1. Gibson, K.H. (Zeneca, Ltd.) *Quinazoline derivs.* WO 9738994.

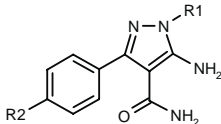
257716

5-Amino-1-*tert*-butyl-3-(4-chlorophenyl)pyrazole-4-carboxamide



C14-H17-Cl-N4-O; Mol wt: 292.77

ACTION – Agent for the treatment of hyperproliferative disorders such as tumors and psoriasis, and immune disorders, a selective inhibitor of p56^{lck} protein tyrosine kinase (IC₅₀ approx. 5 μM or less), with little or no measurable inhibitory activity against protein kinase C (PKC). Within this series of 5-aminopyrazoles, the following are also included:



Compound	R1	R2	Formula
258638	t-Bu	CF ₃	C ₁₅ H ₁₇ F ₃ N ₄ O
258639	t-Bu	CO ₂ Me	C ₁₆ H ₂₀ N ₄ O ₃
258640	i-PrCH(OH)	Me	C ₁₅ H ₂₀ N ₄ O ₂

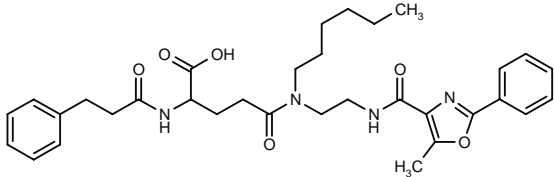
SOURCE – Celltech.

REFERENCES

1. Davis, P.D. et al. (Celltech Therapeut., Ltd.) *5-Aminopyrazoles useful as selective inhibitors of the protein tyrosine kinase p56lck.* WO 9740019.

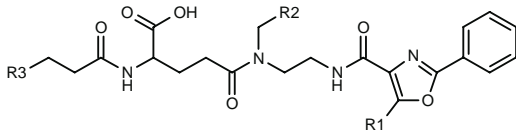
258213

N-Hexyl-*N*-[2-(5-methyl-2-phenyloxazol-4-ylcarboxamido)ethyl]-2-(3-phenylpropionamido)glutaramic acid



C33-H42-N4-O6; Mol wt: 590.72

ACTION – Antineoplastic agent that acts by inhibiting protein phosphatases, particularly serine/threonine phosphatases such as PP1, PP2A and PP3 and dual-specificity phosphatases such as CDC25A and CDC25B. Antiproliferative activity was demonstrated against human breast cancer MDA-MB-231 cells (IC₅₀ = 20 μM). Other compounds from this series of glutaramic acid derivatives include the following:



Compound	R1	R2	R3	Formula
258303	Me	Ph	Ph	C ₃₄ H ₃₆ N ₄ O ₆
258304	Ph	Ph	C ₇ H ₁₅	C ₄₀ H ₄₈ N ₄ O ₆
258305	Ph	C ₅ H ₁₁	C ₇ H ₁₅	C ₃₉ H ₅₄ N ₄ O ₆
258306	Ph	H	C ₇ H ₁₅	C ₃₄ H ₄₄ N ₄ O ₆

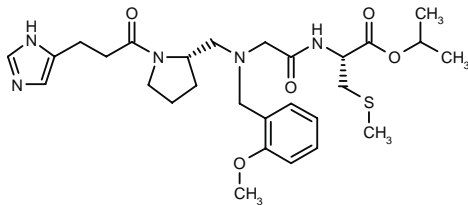
SOURCE – Univ. Pittsburgh, Pittsburgh, PA (US).

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1. Lazo, J.S. et al. (Univ. Pittsburgh) *Phosphatase inhibitors and methods of use thereof.* US 5700821.

258318

N-[1-[3-(1*H*-Imidazol-4-yl)propionyl]pyrrolidin-2(*S*)-yl-methyl]-*N*-(2-methoxybenzyl)glycyl-L-methionine isopropyl ester



C28-H41-N5-O5-S; Mol wt: 559.72

ACTION – Antineoplastic agent, a prodrug of a known protein farnesyltransferase inhibitor that does not have a thiol moiety, reported to exhibit sustained inhibition of this enzyme in white blood cells of dogs and monkeys following a single administration.

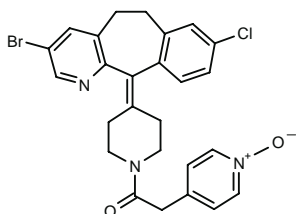
SOURCE – Merck & Co.

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259168

3-Bromo-8-chloro-11-[1-[2-(1-oxidopyridin-4-yl)acetyl]-piperidin-4-ylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine



C26-H23-Br-Cl-N3-O2; Mol wt: 524.84

ACTION – Antineoplastic agent, a selective, nonpeptide, nonsulfhydryl inhibitor of protein farnesyltransferase (IC_{50} = 0.09 μ M in Ha-Ras-CVLS cells) and of H-Ras processing in intact cells (IC_{50} = 0.6 μ M in monkey kidney COS cells). When given orally (10 and 50 mg/kg q.i.d. for 14-21 days), compound significantly inhibited the growth of PT-24 (45 and 81%, respectively), CVLS (52 and 81%, respectively) and human colon DLD-1 tumors (28 and 40%, respectively); after p.o. or i.v. administration (25 mg/kg) it displayed a favorable pharmacokinetic profile, with AUC values of 12.9 μ g.h/ml (p.o.) and 17.3 μ g.h/ml (i.v.), a C_{max} of 8.30 μ g/ml (p.o.) and a $t_{1/2}$ of 48 min (i.v.).

SOURCE – Schering-Plough.

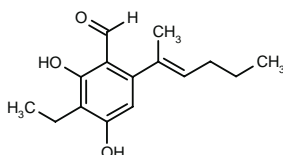
REFERENCES

1. Bishop, W.R. et al. (Schering Corp.) *Tricyclic amide and urea cpds. useful for inhibition of G-protein function and for treatment of proliferative diseases*. WO 9630363.
2. Njoroge, F.G. et al. *Structure-activity relationship of 3-substituted N-(pyridinylacetyl)-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine inhibitors of farnesyl-protein transferase: Design and synthesis of in vivo active antitumor compounds*. J Med Chem 1997, 40(26): 4290.

CRM-51005

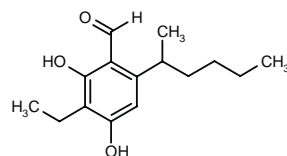
258366

(E)-3-Ethyl-2,4-dihydroxy-6-(1-methyl-1-pentenyl)benzaldehyde



C15-H20-O3; Mol wt: 248.32

ACTION – Potential antiproliferative agent, a phospholipase C (PLC) inhibitor produced by an unidentified fungus strain MT51005. It inhibited bovine brain PLC (IC_{50} = 13.0 μ g/ml) and platelet-derived growth factor (PDGF)-stimulated phosphoinositide (PI) turnover in NIH3T3 γ 1 cells (IC_{50} = 0.8 μ g/ml). The known compound anguillosporal was also isolated from the same source and showed almost the same potency in these tests.



Anguillosporal [258367]: C15-H22-O3

SOURCES – Korea Res. Inst. Biosci. Biotechnol., Taejon (KR); Korea Adv. Inst. Sci. Technol., Taejon (KR).

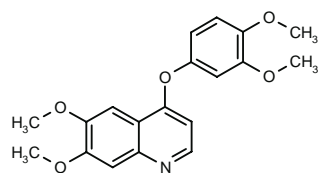
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1. Oh, W.K. et al. *CRM-51005, a new phospholipase C inhibitor produced by unidentified fungal strain MT51005*. J Antibiot 1997, 50(12): 1083.
2. Oh, W.K. et al. *CRM-51005, a new phospholipase C (PLC) inhibitor produced by unidentified fungal strain MT51005*. AFMC Int Med Chem Symp (July 27-Aug 1, Seoul) 1997, Abst PB-24.

Ki-6783

258377

4-(3,4-Dimethoxyphenoxy)-6,7-dimethoxyquinoline



C19-H19-N-O5; Mol wt: 341.36

ACTION – Potent and highly selective inhibitor of platelet-derived growth factor (PDGF) receptor autophosphorylation (IC_{50} = 0.13, 0.07 and 0.15 μ M, respectively, in rat mesangial cells, NIH 3T3 cells and human aortic smooth muscle cells) with no effect against other tyrosine and serine/threonine kinases such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF) and insulin β -receptor tyrosine kinase (IC_{50} > 100 μ M). Ki-6783 was able to inhibit the increase in DNA synthesis and cell proliferation induced by PDGF-BB in rat mesangial cells. The compound also normalized the morphology of v-sis-transfected NIH 3T3 cells. Potentially useful for the treatment of cancer, atherosclerosis, glomerulonephritis and tissue fibrosis.

SOURCE – Kirin Brewery.

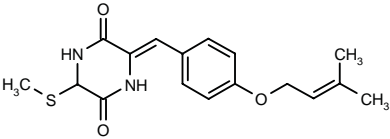
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3. Yagi, M. et al. *Selective inhibition of platelet-derived growth factor (PDGF) receptor autophosphorylation and PDGF-mediated cellular events by a quinoline derivative*. Exp Cell Res 1997, 234(2): 285.

SCH-56396

258361

(Z)-3-[4-(3-Methyl-2-butenyloxy)benzylidene]-6-(methyl-sulfanyl)piperazine-2,5-dione



C17-H20-N2-O3-S; Mol wt: 332.42

Pale yellow powder; m.p. 170-2 °C, $[\alpha]_D^{26} -9.0^\circ$ (c 0.2, CHCl3).

ACTION – Potential antineoplastic agent, an inhibitor of *c-fos* protooncogene induction produced by the fungus *Tolypocladium* sp. (SCF-0729). Compound inhibited serum-stimulated transcription of the human promoter in the *fos/lac* Z reporter gene assay with an IC₅₀ of 15 μM, and it showed cytotoxicity in the MTT assay (IC₅₀ = 39 μM).

SOURCE – Schering-Plough.

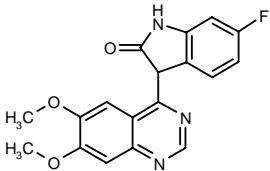
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1. Chu, M. et al. *Sch 56396: A new c-fos proto-oncogene inhibitor produced by the fungus Tolypocladium sp.* J Antibiot 1997, 50(12): 1061.

ANTIANGIOGENIC AGENTS

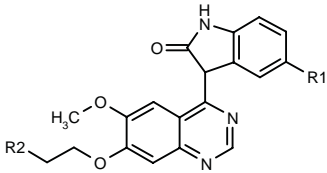
257808

3-(6,7-Dimethoxyquinazolin-4-yl)-6-fluoroindolin-2-one



C18-H14-F-N3-O3; Mol wt: 339.33

ACTION – Agent for the treatment of diseases associated with angiogenesis and/or increased vascular permeability such as cancer, rheumatoid arthritis, diabetes, psoriasis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation and ocular diseases with retinal vessel proliferation, an inhibitor of vascular endothelial growth factor (VEGF) receptor and fibroblast growth factor (FGF) R1 receptor tyrosine kinases, with significantly lower activity against epidermal growth factor (EGF) receptor tyrosine kinase. Other compounds from this series of specifically claimed oxindole derivatives include the following:



Compound	R1	R2	Formula
258935	Br	OMe	C ₂₀ H ₁₈ BrN ₃ O ₄
258936	OH	4-morpholinyl-CH2	C ₂₄ H ₂₆ N ₄ O ₅
258937	SO2NH2	OMe	C ₂₀ H ₂₀ N ₄ O ₆ S
258938	H	OCH2CH2OMe	C ₂₂ H ₂₃ N ₃ O ₅
258939	F	4-morpholinyl-CH2	C ₂₄ H ₂₅ FN ₄ O ₄
258940	CN	1-imidazolyl	C ₂₃ H ₁₈ N ₆ O ₃
258941	H	4-morpholinyl-CH2	C ₂₄ H ₂₆ N ₄ O ₄

SOURCE – Zeneca.

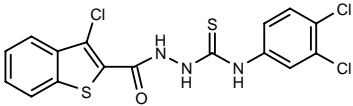
REFERENCES

1. Thomas, A.P. et al. (Zeneca, Ltd.; Zeneca Pharma SA) *Oxindole derivs.* WO 9742187.

MISCELLANEOUS
ANTINEOPLASTIC AGENTS

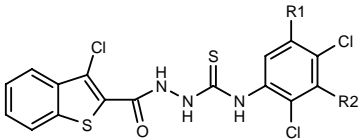
258314

4-(3-Chlorobenzothiophen-2-ylcarbonyl)-1-(3,4-dichlorophenyl)thiosemicarbazide



C16-H10-Cl3-N3-O-S2; Mol wt: 430.75

ACTION – Antineoplastic agent that acts by inhibiting telomerase (IC₅₀ = 12 μM), an enzyme believed to play an important role in the replication of cancer cells and which is highly specific to cancer cells. A representative compound from a series of specifically claimed benzo[*b*]thiophene derivatives, wherein the following are also included:



Compound	R1	R2	Formula
258905	H	Cl	C ₁₆ H ₉ Cl ₄ N ₃ OS ₂
258906	H	H	C ₁₆ H ₁₀ Cl ₃ N ₃ OS ₂
258907	Cl	H	C ₁₆ H ₉ Cl ₄ N ₃ OS ₂

SOURCE – Geron.

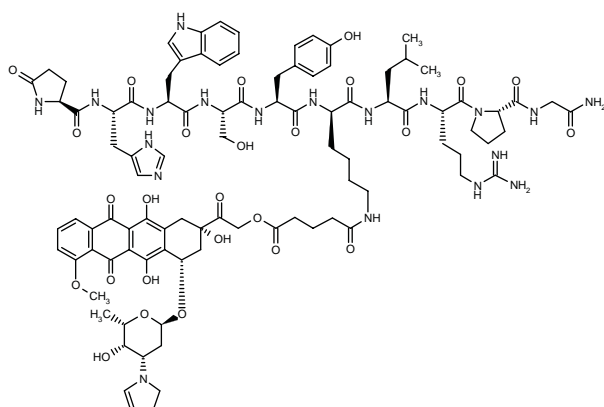
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AN-207*,1

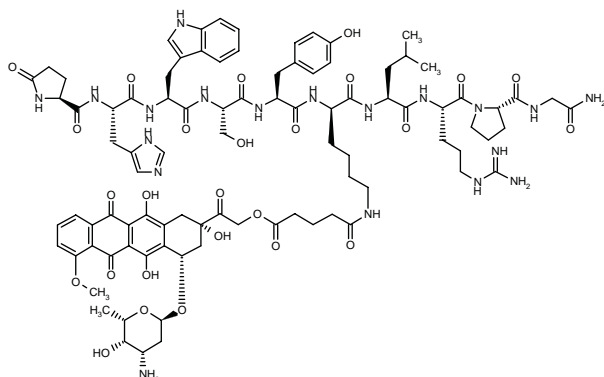
253005

L-Pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-L-N^ε-[4-[3'-desamino-3'-(2,3-dihydro-1H-pyrrol-1-yl)adriamycin-14-O-yl]succinyl]lysyl-L-leucyl-L-arginyl-L-prolyl-L-glycinamide



C95-H121-N19-O26; Mol wt: 1945.11

ACTION – Antineoplastic agent, a hybrid molecule of 2-pyrrolinodoxorubicin (AN-201) conjugated to the carrier agonist [D-Lys⁶]-LHRH targeted to tumors expressing LHRH receptors such as prostatic, mammary, ovarian and endometrial cancers. In mice bearing estrogen-independent murine mammary carcinoma MXT, the optimal dose of 110 nmol/kg i.p. x 2 resulted in a tumor volume reduction of 89% on day 17, without significant toxicity; at a dose of 154 nmol/kg i.p. once weekly for 2 weeks, it resulted in significant tumor-free survival. Both reduction in cell proliferation and increased apoptosis appeared to be involved in its antitumor activity. In rats bearing hormone-dependent Dunning R-3327-H prostate carcinoma, after 5 weeks of treatment with a total dose of 150 nmol/kg, tumor volume decreased from 8.35 ± 1.7 cm³ initially to 4.47 ± 0.8 cm³ (vs. 17.84 ± 2.2 cm³ for control group); tumor weight and tumor burden were also significantly reduced. Another potent cytotoxic LHRH analog containing doxorubicin is:



AN-152^{1,2} [253383]**: C91-H117-N19-H26

SOURCE – Asta Medica.

REFERENCES

1. Schally, A.V. et al. (Asta Medica AG) *Targeted cytotoxic anthracycline analogs*. WO 9719954.
2. Schally, A.W. et al. (Tulane Educational Fund.) *LHRH analogs*. EP 450461.
3. Jungwirth, A. et al. *Regression of rat Dunning R-3327-H prostate carcinoma by treatment with targeted cytotoxic analog of luteinizing hormone-releasing hormone AN-207 containing 2-pyrrolinodoxorubicin*. Int J Oncol 1997, 10(5): 877.
4. Kovacs, M. et al. *Recovery of pituitary function after treatment with a targeted cytotoxic analog of luteinizing hormone-releasing hormone*. Proc Natl Acad Sci USA 1997, 94(4): 1420.
5. Nagy, A. et al. *Cytotoxic analogs of luteinizing hormone-releasing hormone containing doxorubicin or 2-pyrrolinodoxorubicin, a derivative 500-1000 times more potent*. Proc Natl Acad Sci USA 1996, 93(14): 7269.
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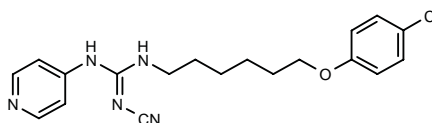
*Identified compound **253005** Drug Data Rep 1997, 19(10): 945.

Identified compound **253383 (see **253005**) Drug Data Rep 1997, 19(10): 945.

CHS-828

258684

N-[6-(4-Chlorophenoxy)hexyl]-N'-cyano-N''-(4-pyridyl)-guanidine



C19-H22-Cl-N5-O; Mol wt: 371.87

White crystals, m.p. 147-8 °C.

ACTION – Antineoplastic agent, a cyanoguanidine derivative devoid of potassium channel-opening activity. Compound displayed potent antiproliferative activity against the resistant small cell lung cancer NYH cell line and MCF-7 cells *in vitro* (IC₅₀ = 2.7 ± 2.0 and 31.0 ± 24.0 nM, respectively) comparable to daunorubicin (IC₅₀ = 3.9 ± 0.9 and 39.0 ± 4.9 nM, respectively) and paclitaxel (IC₅₀ = 4.3 ± 3.3 and 4.9 ± 0.8 nM, respectively), and much lower cytotoxic effects against human lung fibroblasts compared to paclitaxel (IC₅₀ = 40.0 ± 42.4 nM vs. 0.9 ± 0.2 nM); the compound was less active than reference compounds against a number of other tumor cell lines tested. *In vivo*, it showed high activity in rats bearing Yoshida ascites tumors (100% ILS) and induced complete remission in nude mice bearing NYH xenotransplants at doses of 20-50 mg/kg/day p.o. on days 14-28, with no tumor recurrence at 4 weeks in the high-dose group and no effect on body weight; daunorubicin (0.5 mg/kg/day i.p.) showed no activity and paclitaxel (10 mg/kg/day s.c.) induced significant, but not complete, tumor growth inhibition.

SOURCE – Leo.

REFERENCES

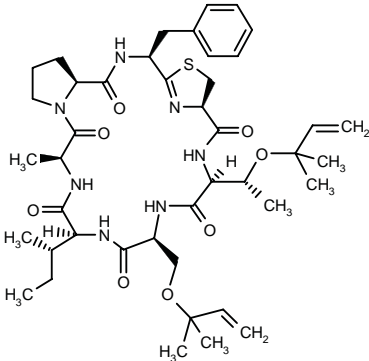
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2. Schou, C. et al. *Novel cyanoguanidines with potent oral antitumor activity*. Bioorg Med Chem Lett 1997, 7(24): 3095.

TRUNKAMIDE A

257261

[3*S*-(3 α ,7 β ,10 α ,13 α ,16 α ,19 α ,24 $\alpha\beta$)]-3-Benzyl-10-[1(*R*)-(1,1-dimethyl-2-propenyloxy)ethyl]-13-(1,1-dimethyl-2-propenyloxymethyl)-19-methyl-16-[1(*S*)-methylpropyl]-7,4-nitriloperhydropyrrolo[2,1-*f*][1,4,7,10,13,16,19]thiahexaazadocosine-1,8,11,14,17,10-hexaone



C43-H63-N7-O8-S; Mol wt: 838.07

ACTION – Antineoplastic cyclic peptide isolated from an ascidian *Lissoclinum* sp., active *in vitro* against murine leukemia P388, human lung carcinoma A-549, human colon carcinoma HT-29 and human melanoma MEL-28 cells (IC₅₀ = 0.5, 0.5, 0.5 and 1.0 μ g/ml, respectively).

SOURCE – Pharma Mar.

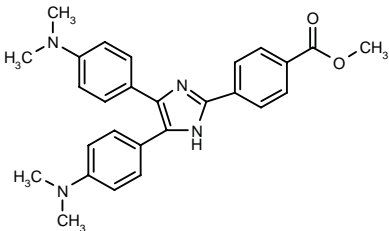
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RESISTANCE MODIFIERS

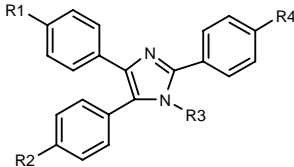
258308

4-[4,5-Bis[4-(dimethylamino)phenyl]-1*H*-imidazol-2-yl]-benzoic acid methyl ester



C27-H28-N4-O2; Mol wt: 440.54

ACTION – Modifier of P-glycoprotein-mediated multidrug resistance (MDR) proven to increase the cytotoxicity of vinblastine (5 μ g/ml) in CEM/VLB1000 and SK/VLB1000 cells with EC₅₀ values of 0.3 and 1.0 μ M, respectively. In addition, it was shown to increase the accumulation of [³H]-vinblastine in CEM/VLB1000 cells with an EC₅₀ of 5.0 μ M. A representative compound from a series of 1,2,4,5-tetra-substituted imidazoles, wherein the following are also included:



Compound	R1=R2	R3	R4	Formula
258876	N(Me)2	H	CH=CHCO2Me	C ₂₉ H ₃₀ N ₄ O ₂
258877	N(Me)2	CH2CH2Ph	OH	C ₃₃ H ₃₄ N ₄ O
258878	OMe	(CH2)5CO2Me	CH=CHCO2Me	C ₃₄ H ₃₆ N ₂ O ₆
258879	OMe	1-imidazolyl-(CH2)3	CH=CHPh	C ₃₇ H ₃₄ N ₄ O ₂
258880	OMe	(CH2)6OMe	CH=CHCO2Me	C ₃₄ H ₃₈ N ₂ O ₅

SOURCE – Ontogen.

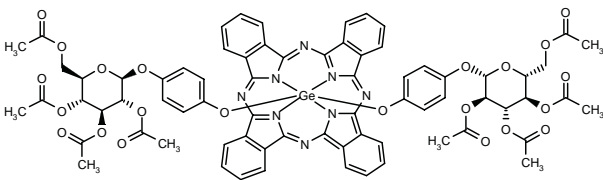
REFERENCES

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RADIATION THERAPY

256657

Bis[4-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)phenolato(1-)]phthalocyaninato(2-)germanium



C72-H62-Ge-N8-O22; Mol wt: 1463.91

ACTION – Germanium–phthalocyanine complex for use in the photodynamic chemotherapy of tumors. Compound is also reported to be of use for the treatment of viral diseases such as Kaposi’s sarcoma, skin disorders such as psoriasis and acne vulgaris, and arteriosclerosis, as well as for viral inactivation of stored blood and for the diagnosis of tumors.

SOURCE – Novartis.

REFERENCES

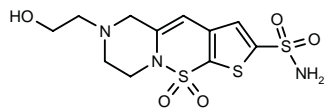
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OCULAR MEDICATIONS

ANTI GLAUCOMA AGENTS

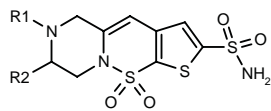
256027

6-(2-Hydroxyethyl)-5,6,7,8-tetrahydropyrazino[1,2-*b*]-thieno[3,2-*e*][1,2]thiazine-2-sulfonamide 10,10-dioxide

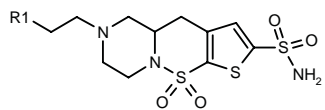


C11-H15-N3-O5-S3; Mol wt: 365.44

ACTION – Agent for the treatment of glaucoma, a carbonic anhydrase inhibitor (CAI) suitable for topical delivery to the eye, and which is thus devoid of the systemic side effects associated with orally administered CAIs. A representative compound from a series of specifically claimed heterocyclic sulfonamides, wherein the following are also included:



Compound	R1	R2	Formula
258048	CH2CH2OMe	H	C ₁₂ H ₁₇ N ₃ O ₅ S ₃
258051	H	CH2OH	C ₁₀ H ₁₃ N ₃ O ₅ S ₃
258052	H	cyclopropyl-COOCH2	C ₁₄ H ₁₇ N ₃ O ₆ S ₃



Compound	R1	Formula
258049	OMe	C ₁₂ H ₁₉ N ₃ O ₅ S ₃
258050	CH2OMe	C ₁₃ H ₂₂ ClN ₃ O ₅ S ₃

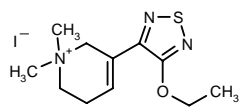
SOURCE – Alcon.

REFERENCES

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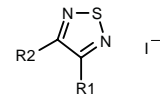
257734

3-(4-Ethoxy-1,2,5-thiadiazol-3-yl)-1,1-dimethyl-1,2,5,6-tetrahydropyridinium iodide

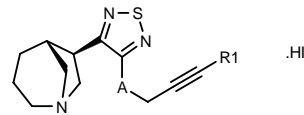


C11-H18-I-N3-O-S; Mol wt: 367.25

ACTION – Peripheral muscarinic cholinergic compound for the treatment of glaucoma, gastrointestinal motility disorders, irritable bowel syndrome, urinary bladder disorders and respiratory disorders. Affinity for muscarinic acetylcholine receptors was demonstrated by its ability to inhibit [³H]-oxotremorine and [³H]-pirenzepine binding in rat cerebral cortex membrane preparations (IC₅₀ = 0.59 and 4.5 nM, respectively). Other specifically claimed azacyclic or azabicyclic compounds include the following:



Compound	R1	R2	Formula
258616	SC6H13	1,1-(Me)2-1,2,5,6-tetrahydro-3-Pyr	C ₁₅ H ₂₆ IN ₃ S ₂
258617	OC6H13	1,1-(Me)2-1,2,5,6-tetrahydro-3-Pyr	C ₁₅ H ₂₆ IN ₃ OS
258618	SBu	1-Me-1-azabicyclo[2.2.2]oct-3-yl	C ₁₄ H ₂₄ IN ₃ S ₂
258619	SBu	endo-1-Me-1-azabicyclo[3.2.1]oct-6-yl	C ₁₄ H ₂₄ IN ₃ S ₂
258620	SC5H11	endo-1-Me-1-azabicyclo[3.2.1]oct-6-yl	C ₁₅ H ₂₆ IN ₃ S ₂
258621	SC5H11	exo-1-Me-1-azabicyclo[3.2.1]oct-6-yl	C ₁₅ H ₂₆ IN ₃ S ₂
258622	SEt	1-Et-1-Me-1,2,5,6-tetrahydro-3-Pyr	C ₁₂ H ₂₀ IN ₃ S ₂
258623	SEt	1,1-(Me)2-1,2,5,6-tetrahydro-3-Pyr	C ₁₁ H ₁₈ IN ₃ S ₂
258624	OEt	1-Et-1-Me-1,2,5,6-tetrahydro-3-Pyr	C ₁₂ H ₂₀ IN ₃ OS



Compound	R1	A	Formula
258625	3-thienyl	O	C ₁₆ H ₁₇ N ₃ OS ₂ .HI
258626	2-thienyl	O	C ₁₆ H ₁₇ N ₃ OS ₂ .HI
258627	Ph	S	C ₁₈ H ₁₉ N ₃ S ₂ .HI

SOURCE – Novo Nordisk.

REFERENCES

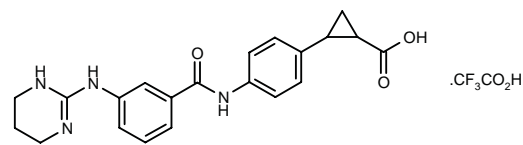
1. Olesen, P.H. and Sauerberg, P. (Novo Nordisk A/S) *Heterocyclic cpds. and their preparation and use*. WO 9740045.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

257147

2-[4-[3-(1,4,5,6-Tetrahydropyrimidin-2-ylamino)benzamido]phenyl]cyclopropanecarboxylic acid trifluoroacetate



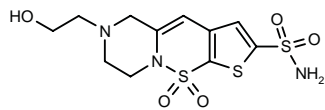
C21-H22-N4-O3.C2-H-F3-O2; Mol wt: 492.45

OCULAR MEDICATIONS

ANTI GLAUCOMA AGENTS

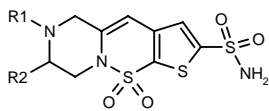
256027

6-(2-Hydroxyethyl)-5,6,7,8-tetrahydropyrazino[1,2-*b*]-thieno[3,2-*e*][1,2]thiazine-2-sulfonamide 10,10-dioxide

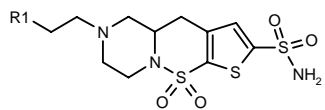


C11-H15-N3-O5-S3; Mol wt: 365.44

ACTION – Agent for the treatment of glaucoma, a carbonic anhydrase inhibitor (CAI) suitable for topical delivery to the eye, and which is thus devoid of the systemic side effects associated with orally administered CAIs. A representative compound from a series of specifically claimed heterocyclic sulfonamides, wherein the following are also included:



Compound	R1	R2	Formula
258048	CH2CH2OMe	H	C ₁₂ H ₁₇ N ₃ O ₅ S ₃
258051	H	CH2OH	C ₁₀ H ₁₃ N ₃ O ₅ S ₃
258052	H	cyclopropyl-COOCH2	C ₁₄ H ₁₇ N ₃ O ₆ S ₃



Compound	R1	Formula
258049	OMe	C ₁₂ H ₁₉ N ₃ O ₅ S ₃
258050	CH2OMe	C ₁₃ H ₂₂ ClN ₃ O ₅ S ₃

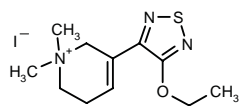
SOURCE – Alcon.

REFERENCES

1. May, J.S. et al. (Alcon Labs., Inc.) *Heterocyclic sulfonamides*. US 5681834.

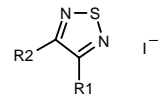
257734

3-(4-Ethoxy-1,2,5-thiadiazol-3-yl)-1,1-dimethyl-1,2,5,6-tetrahydropyridinium iodide

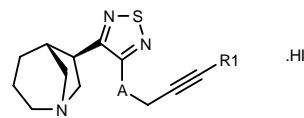


C11-H18-I-N3-O-S; Mol wt: 367.25

ACTION – Peripheral muscarinic cholinergic compound for the treatment of glaucoma, gastrointestinal motility disorders, irritable bowel syndrome, urinary bladder disorders and respiratory disorders. Affinity for muscarinic acetylcholine receptors was demonstrated by its ability to inhibit [³H]-oxotremorine and [³H]-pirenzepine binding in rat cerebral cortex membrane preparations (IC₅₀ = 0.59 and 4.5 nM, respectively). Other specifically claimed azacyclic or azabicyclic compounds include the following:



Compound	R1	R2	Formula
258616	SC6H13	1,1-(Me)2-1,2,5,6-tetrahydro-3-Pyr	C ₁₅ H ₂₆ N ₃ S ₂
258617	OC6H13	1,1-(Me)2-1,2,5,6-tetrahydro-3-Pyr	C ₁₅ H ₂₆ N ₃ OS
258618	SBu	1-Me-1-azabicyclo[2.2.2]oct-3-yl	C ₁₄ H ₂₄ N ₃ S ₂
258619	SBu	endo-1-Me-1-azabicyclo[3.2.1]oct-6-yl	C ₁₄ H ₂₄ N ₃ S ₂
258620	SC5H11	endo-1-Me-1-azabicyclo[3.2.1]oct-6-yl	C ₁₅ H ₂₆ N ₃ S ₂
258621	SC5H11	exo-1-Me-1-azabicyclo[3.2.1]oct-6-yl	C ₁₅ H ₂₆ N ₃ S ₂
258622	SEt	1-Et-1-Me-1,2,5,6-tetrahydro-3-Pyr	C ₁₂ H ₂₀ N ₃ S ₂
258623	SEt	1,1-(Me)2-1,2,5,6-tetrahydro-3-Pyr	C ₁₁ H ₁₈ N ₃ S ₂
258624	OEt	1-Et-1-Me-1,2,5,6-tetrahydro-3-Pyr	C ₁₂ H ₂₀ N ₃ OS



Compound	R1	A	Formula
258625	3-thienyl	O	C ₁₆ H ₁₇ N ₃ OS ₂ .HI
258626	2-thienyl	O	C ₁₆ H ₁₇ N ₃ OS ₂ .HI
258627	Ph	S	C ₁₈ H ₁₉ N ₃ S ₂ .HI

SOURCE – Novo Nordisk.

REFERENCES

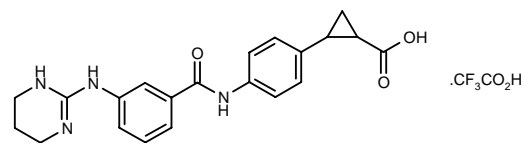
1. Olesen, P.H. and Sauerberg, P. (Novo Nordisk A/S) *Heterocyclic cpds. and their preparation and use*. WO 9740045.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

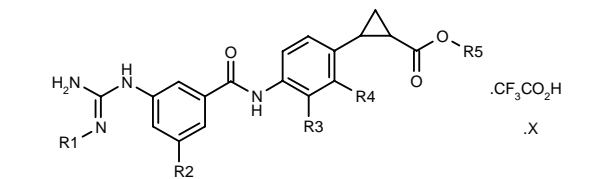
257147

2-[4-[3-(1,4,5,6-Tetrahydropyrimidin-2-ylamino)benzamido]phenyl]cyclopropanecarboxylic acid trifluoroacetate

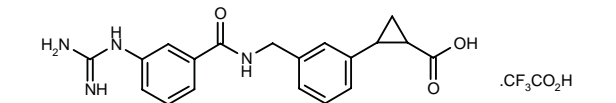


C21-H22-N4-O3.C2-H-F3-O2; Mol wt: 492.45

ACTION – Potent and selective vitronectin ($\alpha_v\beta_3$) receptor antagonist claimed for use in the treatment of disorders such as osteoporosis, tumor metastasis, solid tumor growth, angiogenesis, retinopathy, psoriasis, restenosis and rheumatoid arthritis. Compound gave an IC_{50} of 19.0 nM at the human vitronectin receptor compared to 4800 nM at the human fibrinogen (gpIIb/IIIa) receptor. Other specifically claimed cyclopropyl alkanolic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
257860	H	H	H	H	Et		C ₂₀ H ₂₂ N ₄ O ₃ .C ₂ HF ₃ O ₂
257861	H	H	H	H	H		C ₁₈ H ₁₈ N ₄ O ₃ .C ₂ HF ₃ O ₂
257863	H	H	H	OMe	Et	H ₂ O	C ₂₁ H ₂₄ N ₄ O ₄ .C ₂ HF ₃ O ₂ .H ₂ O
257864	H	H	H	OMe	H		C ₁₉ H ₂₀ N ₄ O ₄ .C ₂ HF ₃ O ₂
257865	H	CF ₃	H	H	H		C ₁₉ H ₁₇ F ₃ N ₄ O ₃ .C ₂ HF ₃ O ₂
257866	CONH ₂	H	H	H	H		C ₁₉ H ₁₉ N ₅ O ₄ .C ₂ HF ₃ O ₂
257867	H	H	F	H	H		C ₁₈ H ₁₇ FN ₄ O ₃ .C ₂ HF ₃ O ₂



257862: C₁₉-H₂₀-N₄-O₃.C₂-H-F₃-O₂

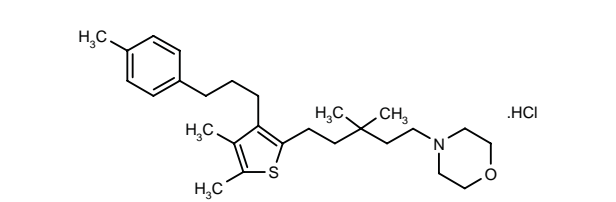
SOURCE – Searle.

REFERENCES

1. Chen, B.B. et al. (G.D Searle & Co.) *Cyclopropyl alkanolic acid derivs.* WO 9736858.

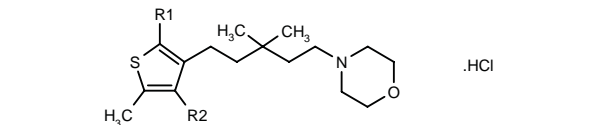
258309

5-[3,3-Dimethyl-5-(4-morpholinyl)pentyl]-2,3-dimethyl-4-[3-(4-methylphenyl)propyl]thiophene hydrochloride

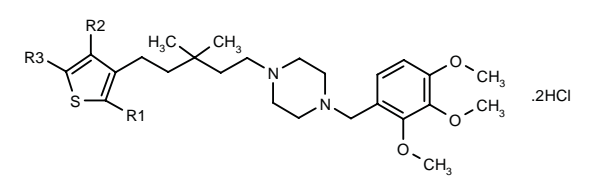


C₂₇-H₄₁-N-O-S.HCl; Mol wt: 464.15

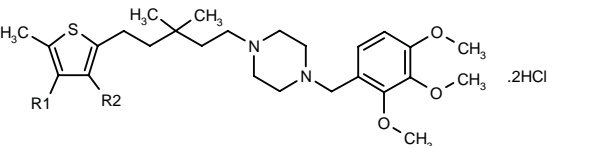
ACTION – Agent for the treatment of osteoporosis with bone resorption-inhibitory activity. Other thiophene compounds include the following:



Compound	R1	R2	Formula
258881	Me	(CH ₂) ₃ Ph	C ₂₆ H ₃₉ NOS.HCl
258885	4-Me-Ph(CH ₂) ₃	H	C ₂₆ H ₃₉ NOS.HCl



Compound	R1	R2	R3	Formula
258882	Me	(CH ₂) ₃ Ph	Me	C ₃₆ H ₅₂ N ₂ O ₃ S .2HCl
258884	Me	H	4-Me-Ph(CH ₂) ₃	C ₃₆ H ₅₂ N ₂ O ₃ S .2HCl
258886	4-Me-Ph(CH ₂) ₃	H	Me	C ₃₆ H ₅₂ N ₂ O ₃ S .2HCl



Compound	R1	R2	Formula
258883	Me	4-Me-Ph(CH ₂) ₃	C ₃₇ H ₅₄ N ₂ O ₃ S .2HCl
258887	4-Me-Ph(CH ₂) ₃	H	C ₃₆ H ₅₂ N ₂ O ₃ S .2HCl
258888	H	4-Me-Ph(CH ₂) ₃	C ₃₆ H ₅₂ N ₂ O ₃ S .2HCl

SOURCE – ADIR.

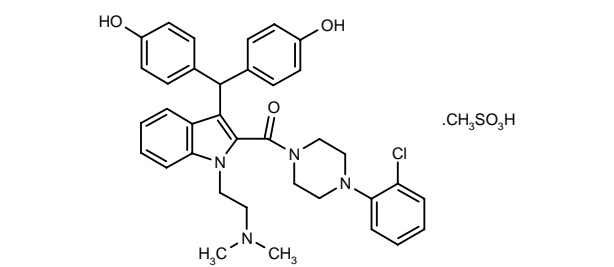
REFERENCES

1. Wierzbicki, M. et al. (ADIR et Cie.) *Thiophene cpds.* US 5703074.

KW-8232^{1,2,4}

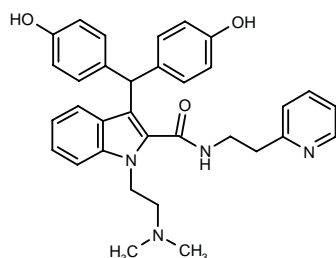
227226

[4-(2-Chlorophenyl)-1-piperazinyl][3-[bis(4-hydroxyphenyl)methyl]-1-[2-(dimethylamino)ethyl]-1*H*-indol-2-yl]methanone methanesulfonate



C₃₆-H₃₇-Cl-N₄-O₃.C-H₄-O₃-S; Mol wt: 705.27

ACTION – Agent for the treatment of osteoporosis, a potent, water-soluble inhibitor of bone resorption, as shown *in vitro* ($IC_{50} = 11.5 \mu\text{mol/l}$) and *in vivo* by the prevention of bone loss induced by ovariectomy in rats; at a dose of 10 mg/kg/day p.o. for 3 weeks, it nearly completely inhibited bone loss and was more potent than KF-18485 and KF-16710 (93, 45 and 36% inhibition, respectively). Another related compound is:



KF-25121^{3,4} [248241]: C33-H34-N4-O3

SOURCE – Kyowa Hakko.

REFERENCES

1. Kato, N. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Indole derivs. preparation*. JP 97100278,.
2. Machii, D. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Indole deriv.* EP 741132, WO 9519343.
3. Machii, D. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Indole derivs.* WO 9703964.
4. Machii, D. et al. *Synthesis of novel antiosteoporotic agents. 3. Synthesis and pharmacological effects of KW-8232 and related derivatives*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-24.

ZG-2807A

257846

Acetyl-tryptophyl-isovalyl-glutaminy-(2-aminoisobutyryl)-leucyl-threonyl-(2-aminoisobutyryl)-isoleucyl-(2-aminoisobutyryl)-prolyl-glutaminy-(2-aminoisobutyryl)-prolyl-(4-methyl)prolyl-phenylalanyl-glycine

C88-H131-N19-O21; Mol wt: 1791.12

ACTION – Small-peptide calcitonin mimetic with bone resorption-inhibitory activity, isolated from a culture of *Acremonium rutilum* W. Gams ZG 2807 (CBS 650.94). It was found to inhibit parathyroid hormone-induced bone resorption in mouse calvariae with an EC_{50} value of 33.2 μM , as measured by inhibition of calcium release; EC_{50} for human calcitonin is in the range 0.2-0.5 nM. Another related calcitonin mimetic is:

Acetyl-tryptophyl-isovalyl-glutaminy-(2-aminoisobutyryl)-leucyl-threonyl-(2-aminoisobutyryl)-isoleucyl-(2-aminoisobutyryl)-prolyl-glutaminy-(2-aminoisobutyryl)-prolyl-(4-methyl)prolyl-phenylalanine

ZG-2807B [258120]; C86-H128-N18-O20

SOURCE – ZymoGenetics.

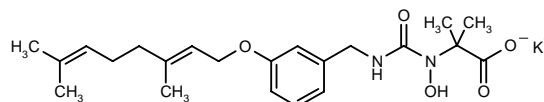
REFERENCES

1. McKernan, P.A. et al. (ZymoGenetics, Inc.) *Native calcitonin mimetics*. US 5698521.

TREATMENT OF LIPOPROTEIN DISORDERS

258384

2-[3-[3-[3,7-Dimethylocta-2(*E*),6-dienyloxy]benzyl]-1-hydroxyureido]-2-methylpropionic acid potassium salt



C22-H31-K-N2-O5; Mol wt: 442.60

ACTION – Squalene synthase inhibitor from a series of farnesyl diphosphate mimics and analogs, identified as a nonphosphorus-containing mimic. It inhibited squalene synthase from rat liver microsomes with an IC_{50} of 0.23 μM .

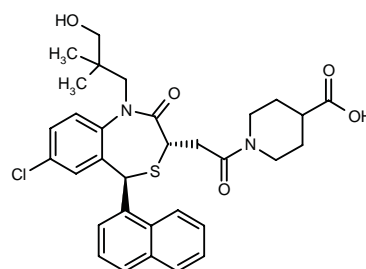
SOURCE – Novartis.

REFERENCES

1. Wattanasin, S. et al. *N-Hydroxyglycine derivatives as novel inhibitors of squalene synthase*. Bioorg Med Chem Lett 1997, 7(23): 3039.

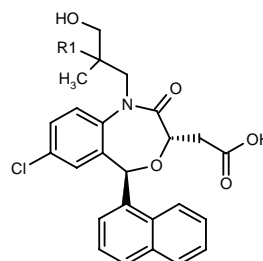
258743

***trans*-1-[2-[7-Chloro-1-(3-hydroxy-2,2-dimethylpropyl)-5-(1-naphthyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzothiazepin-3-yl]acetyl]piperidine-4-carboxylic acid**



C32-H35-Cl-N2-O5-S; Mol wt: 595.15

ACTION – Agent for the treatment of hypercholesterolemia, hypertriglyceridemia, atherosclerosis, fungal infections, acne and Alzheimer's disease with squalene synthase-inhibitory activity. Other compounds from this series of benzoxazepinones and benzothiazepinones include the following:



Compound	R1	Formula
259239	CH2OH	C ₂₆ H ₂₆ ClNO ₆
259240	Me	C ₂₆ H ₂₆ ClNO ₅

SOURCE – Pfizer.

REFERENCES

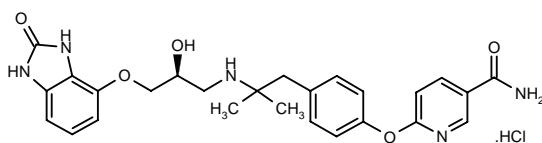
1. Bell, A.S. et al. (Pfizer, Inc.) *Squalene synthetase inhibitors*. EP 814080.

ANTI OBESITY DRUGS

LY-362884

255227

6-[4-[2-[2(*S*)-Hydroxy-3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yloxy)propylamino]-2-methylpropyl]phenoxy]pyridine-3-carboxamide hydrochloride



C26-H29-N5-O5.HCl; Mol wt: 528.01

ACTION – Potent human β_3 -adrenoceptor agonist ($h\beta_3$: $EC_{50} = 30.0 \pm 10$ nM in a whole-cell cAMP accumulation assay; intrinsic activity [IA] = $98 \pm 12\%$ [isoproterenol = 100%]) with antagonist activity at β_1 - and β_2 -adrenoceptors. It displayed potent lipolytic activity *in vitro* in adipose tissue from obese patients and *in vivo* in the Avy/a viable yellow mouse at 25 mg/kg p.o. or s.c. Potentially useful in the treatment of obesity and non-insulin-dependent diabetes mellitus (NIDDM).

SOURCE – Lilly.

REFERENCES

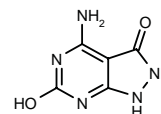
1. Bell, M.G. et al. (Eli Lilly & Co.) *Selective β_3 adrenergic agonists*. EP 764640, WO 9710825.
2. Dananberg, J. *The sympathetic nervous system, β_3 -adrenergic receptor agonists and insulin resistance*. IBC 2nd Int Conf Insulin Resist. Novel Drug Dev Strategies Type II Diabetes Obesity (Oct 6-7, Philadelphia) 1997.
3. Shuker, A.J. et al. *Selective β_3 receptor agonists and beta adrenergic modulators for the treatment of obesity and NIDDM*. 214th ACS Natl Meet (Sep 7-11, Las Vegas) 1997, Abst MEDI 261.
4. Shuker, A.J. *The discovery of selective β_3 receptor agonists and beta adrenergic modulators for the treatment of NIDDM and obesity*. IBC 2nd Int Conf Insulin Resist. Novel Drug Dev Strategies Type II Diabetes Obesity (Oct 6-7, Philadelphia) 1997.
5. Siegel, M.G. et al. *The development of a potent, selective β_3 adrenergic receptor agonist using combinatorial chemistry*. 214th ACS Natl Meet (Sept 7-11, Las Vegas) 1997, Abst MEDI 260.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

HYDROXYAKALONE

257317

4-Amino-6-hydroxy-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-one



C5-H5-N5-O2; Mol wt: 167.13

Colorless powder.

ACTION – Potent xanthine oxidase inhibitor isolated from the fermentation broth of *Agrobacterium aurantiacum* N-81106, with activity stronger than that of alalone and comparable to that of allopurinol ($IC_{50} = 4.6, 16.9$ and 4.0 μ M, respectively, against bovine enzyme). Potentially useful for the treatment of disorders associated with hyperuricemia such as gout.

SOURCE – Kyowa Hakko.

REFERENCES

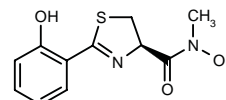
1. Izumi, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *New substance hydroxyakalone, and its use*. JP 96188580.
2. Izumida, H. et al. *Hydroxyakalone, a novel xanthine oxidase inhibitor produced by a marine bacterium, Agrobacterium aurantiacum*. J Antibiot 1997, 50(11): 916.

DIAGNOSTIC AGENTS

257166

N-Hydroxy-2-(2-hydroxyphenyl)-*N*-methyl-4,5-dihydrothiazole-4(*R*)-carboxamide

2-(2-Hydroxyphenyl)-*N*-methyl-4,5-dihydrothiazole-4(*R*)-carboxhydroxamic acid



C11-H12-N2-O3-S; Mol wt: 252.29

ACTION – Trivalent metal chelator capable of forming metal ion complexes with high solubility and good tolerability useful as contrast agents in X-ray, radionuclide, ultrasound and/or magnetic resonance imaging (MRI) diagnostics. Other specifically claimed thiazoline acid derivatives include the following:

SOURCE – Pfizer.

REFERENCES

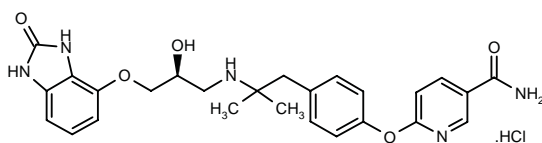
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ANTI OBESITY DRUGS

LY-362884

255227

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C26-H29-N5-O5.HCl; Mol wt: 528.01

ACTION – Potent human β_3 -adrenoceptor agonist ($h\beta_3$: $EC_{50} = 30.0 \pm 10$ nM in a whole-cell cAMP accumulation assay; intrinsic activity [IA] = $98 \pm 12\%$ [isoproterenol = 100%]) with antagonist activity at β_1 - and β_2 -adrenoceptors. It displayed potent lipolytic activity *in vitro* in adipose tissue from obese patients and *in vivo* in the Avy/a viable yellow mouse at 25 mg/kg p.o. or s.c. Potentially useful in the treatment of obesity and non-insulin-dependent diabetes mellitus (NIDDM).

SOURCE – Lilly.

REFERENCES

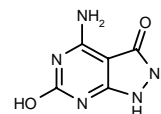
1. Bell, M.G. et al. (Eli Lilly & Co.) *Selective β_3 adrenergic agonists*. EP 764640, WO 9710825.
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3. Shuker, A.J. et al. *Selective β_3 receptor agonists and beta adrenergic modulators for the treatment of obesity and NIDDM*. 214th ACS Natl Meet (Sep 7-11, Las Vegas) 1997, Abst MEDI 261.
4. Shuker, A.J. *The discovery of selective β_3 receptor agonists and beta adrenergic modulators for the treatment of NIDDM and obesity*. IBC 2nd Int Conf Insulin Resist. Novel Drug Dev Strategies Type II Diabetes Obesity (Oct 6-7, Philadelphia) 1997.
5. Siegel, M.G. et al. *The development of a potent, selective β_3 adrenergic receptor agonist using combinatorial chemistry*. 214th ACS Natl Meet (Sept 7-11, Las Vegas) 1997, Abst MEDI 260.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

HYDROXYAKALONE

257317

4-Amino-6-hydroxy-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-one



C5-H5-N5-O2; Mol wt: 167.13

Colorless powder.

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SOURCE – Kyowa Hakko.

REFERENCES

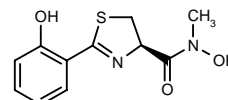
1. Izumi, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *New substance hydroxyakalone, and its use*. JP 96188580.
2. Izumida, H. et al. *Hydroxyakalone, a novel xanthine oxidase inhibitor produced by a marine bacterium, Agrobacterium aurantiacum*. J Antibiot 1997, 50(11): 916.

DIAGNOSTIC AGENTS

257166

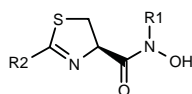
N-Hydroxy-2-(2-hydroxyphenyl)-*N*-methyl-4,5-dihydrothiazole-4(*R*)-carboxamide

2-(2-Hydroxyphenyl)-*N*-methyl-4,5-dihydrothiazole-4(*R*)-carboxhydroxamic acid



C11-H12-N2-O3-S; Mol wt: 252.29

ACTION – Trivalent metal chelator capable of forming metal ion complexes with high solubility and good tolerability useful as contrast agents in X-ray, radionuclide, ultrasound and/or magnetic resonance imaging (MRI) diagnostics. Other specifically claimed thiazoline acid derivatives include the following:



Compound	R1	R2	Formula
257884	H	2-OH-Ph	C ₁₀ H ₁₀ N ₂ O ₃ S
257885	Me	2-OH-1-Naph	C ₁₅ H ₁₄ N ₂ O ₃ S
257886	H	2-OH-1-Naph	C ₁₄ H ₁₂ N ₂ O ₃ S
257887	Me	3-OH-2-Naph	C ₁₅ H ₁₄ N ₂ O ₃ S
257888	H	3-OH-2-Naph	C ₁₄ H ₁₂ N ₂ O ₃ S

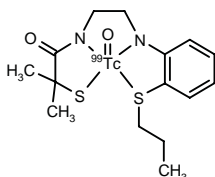
SOURCE – Univ. Florida, Gainesville, FL (US).

REFERENCES

1. Bergeron, R.J. Jr. (Univ. Florida) *Thiazoline acid derivs.* WO 9736885.

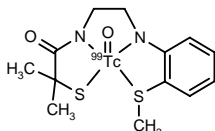
257263

[2-Methyl-*N*-[2-[2-(propylsulfanyl)phenylamino]ethyl]-2-sulfanylpropionamidate(3-)-*N,N',S,S'*]oxotechnetium-(^{99m}Tc)



C15-H21-N2-O2-S2-⁹⁹Tc ; Mol wt: 424.46

ACTION – Lipophilic, neutral technetium-99m complex potentially useful as a radiopharmaceutical diagnostic agent, particularly for brain imaging. Studies in rats showed that it crosses the blood–brain barrier and is retained in the brain. Another specifically claimed complex is:



258123: C13-H17-N2-O2-S2-⁹⁹Tc

SOURCE – Nycomed Amersham.

REFERENCES

1. MacWhorter, S.E. et al. (Amersham Intl. plc) *Diagnostic radiopharmaceutical compound (That)*. US 5690904.

MOT-12

257186

ACTION – Novel protein for the diagnosis and treatment of MOT-12-related conditions, particularly insulin-dependent diabetes. This protein is a receptor-type protein tyrosine kinase phosphatase previously identified as RPTP IA-2, whose expression is restricted to adult brain and pancreas in neurosecretory cell types.

SOURCE – Sugen.

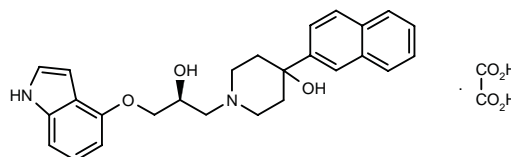
REFERENCES

1. Plowman, G.D. (Sugen, Inc.) *Protein MOT12 and diagnosis of insulin-dependent diabetes.* WO 9736918.

TREATMENT OF POISONING AND DRUG DEPENDENCY

258745

1-[4-Hydroxy-4-(2-naphthyl)piperidin-1-yl]-3-(1*H*-indol-4-yl)-2(*S*)-propanol oxalate



C26-H28-N2-O3.C2-H2-O4; Mol wt: 506.55

ACTION – Agent with dual 5-HT_{1A} receptor antagonist-activity and 5-HT reuptake-inhibitory activity, reported to lack the mutagenic potential of structurally related compounds. Potentially useful for alleviating the symptoms of nicotine or tobacco withdrawal, as well as for the treatment of depression and anxiety.

SOURCE – Lilly.

REFERENCES

1. Koch, D.J. and Rocco, V.P. (Eli Lilly & Co.) *Indole derivs. as 5-HT_{1A} antagonists and as inhibitors of serotonin reuptake.* EP 814084, WO 9748698.

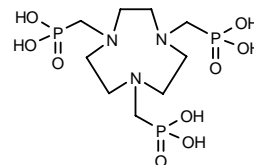
FEROFIX A

258386

[(Hexahydro-1*H*-1,4,7-triazocine-1,4,7-triyl)tris(methylene)]trisphosphonic acid

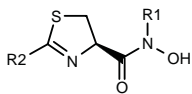
1,4,7-Tris(phosphonomethyl)-1,4,7-triazacyclononane

IRC-011



C9-H24-N3-O9-P3; Mol wt: 411.22

ACTION – Synthetic hexadentate iron chelator, a substituted polyaza compound that shows higher affinity for Fe(III) compared to deferoxamine, is expected to be resistant to *in vivo* catabolism, preferentially interacts with reticuloendothelial iron derived from red blood cell breakdown and shows selective urinary excretion. Potentially useful for protecting organs from peroxidative damage in transfusional iron overload, and also as a lead compound for the development of more lipophilic chelators showing improved interactions with hepatocellular iron stores and better oral activity.



Compound	R1	R2	Formula
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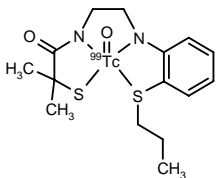
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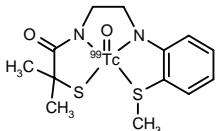
257263

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SOURCE – Sugen.

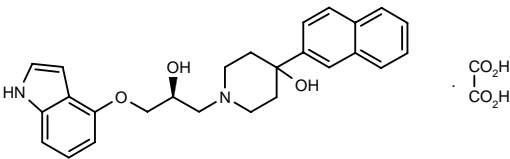
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TREATMENT OF POISONING AND DRUG DEPENDENCY

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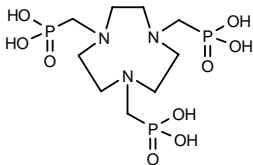
FEROFIX A

258386

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1,4,7-Tris(phosphonomethyl)-1,4,7-triazacyclononane

IRC-011



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SOURCE – Israel Resources.

REFERENCES

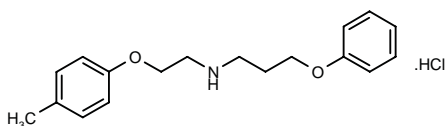
1. Winchell, H.S. et al. (Concat, Ltd.) *Cpds. with chelation affinity and selectivity for first transition series elements, and their use in medical therapy and diagnosis*. WO 9701360.

2. Rivkin, G. et al. *IRC011, a new synthetic chelator with selective interaction with catalytic red blood cell iron: Evaluation in hypertransfused rats with hepatocellular and reticuloendothelial radioiron probes and in iron-loaded rat heart cells in culture*. Blood 1997, 90(10): 4180.

PHARMACOLOGICAL TOOLS

258688

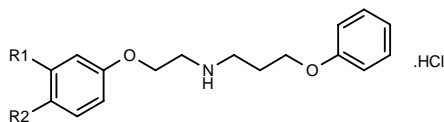
N-[2-(4-Methylphenoxy)ethyl]-*N*-(3-phenoxypropyl)amine hydrochloride



C18-H23-N-O2.HCl; Mol wt: 321.85

M.p. 210-5 °C.

ACTION – Potent and selective dopamine D₄ receptor antagonist, as shown in functional and binding assays (K_i = 0.52, 268 and 169 nM, respectively, for cloned human D₄, D₂ and D₃ receptors; IC₅₀ = 1.5 nM for inhibition of quinpirole-induced mitogenesis in D₄-transfected CHO 10001 cells). Potentially useful as a tool for exploring the role of the D₄ receptor in schizophrenia. Other (aryloxy)-alkylamines are:



Compound	R1	R2	Formula
258693	H	Cl	C ₁₇ H ₂₀ ClNO ₂ .HCl
258694	Cl	Me	C ₁₈ H ₂₂ ClNO ₂ .HCl

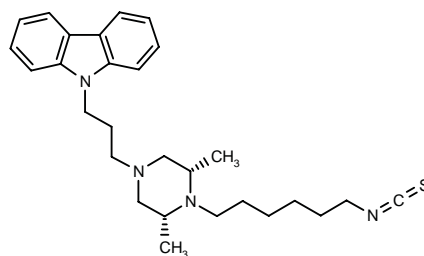
SOURCE – Warner-Lambert.

REFERENCES

1. Unangst, P.C. et al. *(Aryloxy)alkylamines as selective human dopamine D₄ receptor antagonists: Potential antipsychotic agents*. J Med Chem 1997, 40(25): 4026.

259177

cis-9-[3-[3,5-Dimethyl-4-(6-isothiocyanatohexyl)piperazin-1-yl]propyl]carbazole



C28-H38-N4-S; Mol wt: 462.70

Oily solid; hydrochloride salt, m.p. 210-2 °C (*decomp.*).

ACTION – Rimcazole analog that binds with high affinity to the low-affinity site on the dopamine transporter (IC₅₀ = 86.7 nM) in a monophasic and irreversible manner, with selectivity for the dopamine transporter over either σ₁ or σ₂ sites (IC₅₀ = 707 and 211 nM, respectively). Potentially useful as a tool for studying the significance of this low-affinity dopamine transporter site, and also as a lead for novel treatments for cocaine abuse.

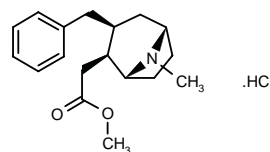
SOURCES – Natl. Inst. Arthritis, Diabetes, Digest. Kidney Dis., Bethesda, MD (US); Natl. Inst. Drug Abuse, Baltimore, MD (US).

REFERENCES

1. Husbands, S.M. et al. *Isothiocyanate derivatives of 9-[3-(cis-3,5-dimethyl-1-piperazinyl)propyl]carbazole (rimcazole): Irreversible ligands for the dopamine transporter*. J Med Chem 1997, 40(26): 4340.

259180

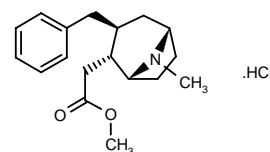
(-)-(1*R*,2*S*,3*S*,5*S*)-2-[3-Benzyl-8-methyl-8-azabicyclo-[3.2.1]oct-2-yl]acetic acid methyl ester hydrochloride



C18-H25-N-O2.HCl; Mol wt: 323.86

M.p. 196-8 °C, [α]_D²⁵ -26° (*c* 0.1, EtOH).

ACTION – Dopamine uptake inhibitor belonging to a new class of cocaine analogs that shows high affinity for the high-affinity binding site on the dopamine transporter (K_i = 33 nM) and produces potent dopamine uptake inhibition (IC₅₀ = 161 nM). Another compound from this series of 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)methyl]tropane derivatives is:



259181: C18-H25-N-O2.HCl

SOURCE – Israel Resources.

REFERENCES

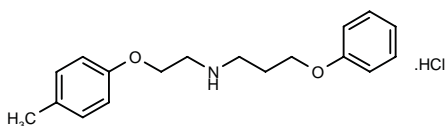
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PHARMACOLOGICAL TOOLS

258688

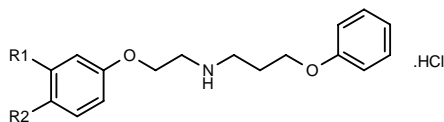
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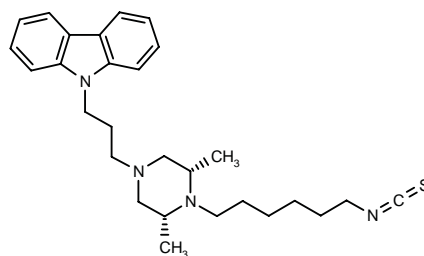
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259177

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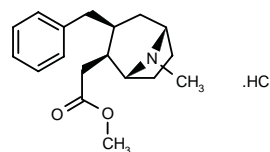
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259180

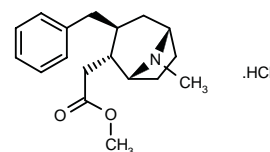
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259181: C18-H25-N-O2.HCl

SOURCES – Univ. New Orleans, New Orleans, LA (US); Xavier Univ. Louisiana, New Orleans, LA (US).

REFERENCES

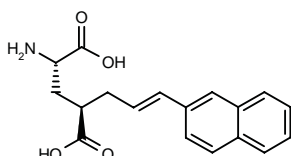
1. Lomenzo, S.A. et al. *Synthesis, structure, dopamine transporter affinity, and dopamine uptake inhibition of 6-alkyl-3-benzyl-2-[(methoxycarbony)methyl]tropane derivatives*. J Med Chem 1997, 40(26): 4406.

LY-339434

258163

(2*S*,4*R*)-4-[3-(2-Naphthyl)-2(*E*)-propenyl]glutamic acid

(2*S*,4*R*)-2-Amino-4-carboxy-7-(2-naphthyl)-6(*E*)-heptenoic acid



C18-H19-N-O4; Mol wt: 313.35

ACTION – Selective kainate GluR5 receptor agonist, as shown in binding studies using HEK293 cells transfected with human receptors (K_i approx. 15 nM at GluR5 vs. > 10 μ M at GluR1, GluR2, GluR4 and GluR6) and in functional studies in rat dorsal root ganglion neurons (EC_{50} = 0.8 ± 0.2 μ M). Potentially useful for elucidating the role of GluR5 receptors in the CNS.

SOURCES – Allelix Biopharmaceuticals; Lilly.

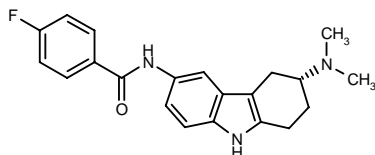
REFERENCES

1. Small, B.G. et al. LY339434, a GluR5-selective kainate receptor agonist. Brit J Pharmacol 1997, 122(Suppl.): Abst 59P.

LY-344864

257321

(*R*)-*N*-[3-(Dimethylamino)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl]-4-fluorobenzamide



C21-H22-F-N3-O; Mol wt: 351.42

ACTION – Potent and selective 5-HT_{1F} receptor agonist (K_i = 6 nM against [³H]-5-HT binding) whose affinity for the 5-HT_{1F} receptor is at least 88-fold greater than for other 5-HT and nonserotonergic binding sites. It demonstrated full agonist activity and potency equal to 5-HT in inhibiting forskolin-stimulated cAMP formation in cells transfected with the human receptor (EC_{50} = 3 nM; maximum inhibition = 98.5% that produced by 5-HT). In rats, at a dose of 1 mg/kg i.v. it gave plasma levels greatly exceeding the K_i in binding assays for at least 8 h, with stable levels in cortex for at least 6 h. It potentially inhibited neurogenic dural inflammation in rats (ID_{50} = 2.1 ng/kg p.o., 0.6 ng/kg i.v.). Potentially useful as a pharmacological tool for elucidating the physiological role of this receptor.

SOURCE – Lilly.

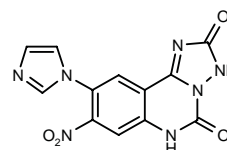
REFERENCES

1. Flaugh, M.E. et al. (Eli Lilly & Co.) 6-Subst.-1,2,3,4-tetrahydro-9*H*-carbazoles and 7-subst.-10*H*-cyclohepta(7,6-*b*)indoles. CA 2179678, EP 749962.
2. Phebus, L.A. et al. Characterization of LY344864 as a pharmacological tool to study 5-HT_{1F} receptors: Binding affinities, brain penetration and activity in the neurogenic dural inflammation model of migraine. Life Sci 1997, 61(21): 2117.

RO-48-8587

258157

9-(1-Imidazolyl)-8-nitro-1,2,4-triazolo[1,5-*c*]quinazoline-2,5(3*H*,6*H*)-dione



C12-H7-N7-O4; Mol wt: 313.23

ACTION – The most potent and selective AMPA receptor antagonist reported to date (K_i = 4 nM). The compound showed moderate neuroprotective activity in a focal cerebral ischemia model and anticonvulsant properties *in vivo*. It is currently the radioligand of choice for studies on the subtype selectivity of AMPA antagonists.

SOURCE – Roche.

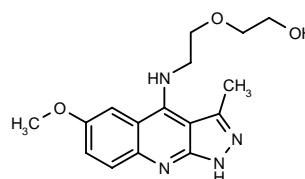
REFERENCES

1. Büttelmann, B. et al. (F. Hoffmann-La Roche AG) Tricyclic dicarbonyl derivs. EP 760819, JP 97506634, US 5688803, WO 9532205.
2. Richards, J.G. et al. *In vitro* binding characteristics of a potent, selective AMPA receptor antagonist, [³H]Ro 48-8587, in rat brain. Brit J Pharmacol 1997, 122(Suppl.): Abst 10P.
3. Richards, J.G. et al. *In vitro* binding characteristics of a potent, selective AMPA receptor antagonist [³H]Ro 48-8587 in rat brain. Soc Neurosci Abstr 1997, 23(Part 1): Abstr 370.16.

SCH-51344

258526

2-[2-(6-Methoxy-3-methyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-ylamino)ethoxy]ethanol



C16-H20-N4-O3; Mol wt: 316.36

ACTION – Inhibitor of *ras* transformation that acts by a novel mechanism distinct from the extracellular signal-regulated kinase (ERK)-dependent Ras signaling pathway. The compound is able to reverse several critical aspects of *ras* transformation and is not cytotoxic; it was shown to inhibit the anchorage-independent growth of a number of oncogene-transformed cells including human tumor cell lines. Potentially useful as a tool for elucidating pathways that affect transformation by the *ras* gene. The identification of the specific target protein inhibited by title compound may provide a novel therapeutic target.

SOURCE – Schering-Plough.

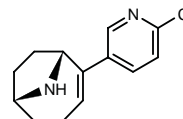
REFERENCES

1. Afonso, A. et al. 4-Substd. pyrazoloquinoline derivs. US 5608067.
2. Kumar, C.C. et al. SCH 51344 inhibits *ras* transformation by a novel mechanism. Cancer Res 1995, 55(21): 5106.
3. Kumar, C.C. Inhibition of RAS-transformation by SCH51344. Jpn J Cancer Chemother 1997, 24(11): 1503.
4. Walsh, A.B. et al. SCH 51344-induced reversal of RAS-transformation is accompanied by the specific inhibition of the RAS and RAC-dependent cell morphology pathway. Oncogene 1997, 15(21): 2553.

UB-165

257309

(1*R*,5*S*)-2-(6-Chloropyridin-3-yl)-9-azabicyclo[4.2.1]non-2-ene



C13-H15-Cl-N2; Mol wt: 234.73

ACTION – Nicotinic acetylcholine (nACh) receptor agonist, an anatoxin-a and epibatidine hybrid with an absolute configuration corresponding to that of natural anatoxin-a. The compound is a potent, enantiospecific ligand for the high-affinity nicotine binding site in rat brain, with activity intermediate between that of epibatidine and anatoxin-a ($IC_{50} = 0.34 \pm 0.02$, 0.041 ± 0.01 and 2.49 ± 0.41 nM, respectively; $K_i = 0.17$, 0.021 and 1.25 nM, respectively).

SOURCES – Univ. Bath, Bath (GB); Univ. Bristol, Bristol (GB).

REFERENCES

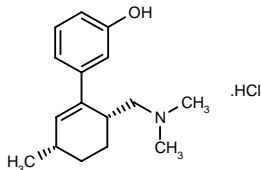
1. Wright, E. et al. Synthesis of UB-165: A novel nicotinic ligand and anatoxin-a/epibatidine hybrid. Bioorg Med Chem Lett 1997, 7(22): 2867.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

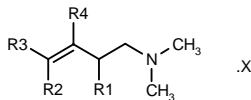
256331

(–)-(3*S*,6*R*)-3-[6-(Dimethylaminomethyl)-3-methyl-1-cyclohexenyl]phenol hydrochloride



C16-H23-N-O.HCl; Mol wt: 281.82

ACTION – Analgesic agent structurally related to tramadol, shown to be more potent than tramadol in the phenylbenzoquinone-induced writhing test in mice (ED₅₀ = 0.90 mg/kg i.v. vs. 3.68 mg/kg i.v. for tramadol). Other related compounds include the following:



Compound	R1	R2	R3	R4	X	Isomer	Formula
259577	Me	H	Me	3-OH-Ph	HCl		C ₁₄ H ₂₁ NO.HCl
259578	Me	H	Me	3-OH-Ph	HCl	S	C ₁₄ H ₂₁ NO.HCl
259579	Me	H	Me	3-OH-Ph	HCl	R	C ₁₄ H ₂₁ NO.HCl
259580	Me	H	Me	3-(2-AcO-Ph-COO)-Ph			C ₂₃ H ₂₇ NO ₄
259581	Me	H	Me	6-OH-2-Naph	HCl		C ₁₈ H ₂₃ NO.HCl
259582	Me	H	Et	3-MeO-Ph			C ₁₆ H ₂₅ NO
259583	Me	H	Et	3-OH-Ph	HCl		C ₁₅ H ₂₃ NO.HCl
259584	Me	Me	Me	3-OH-Ph	HCl		C ₁₅ H ₂₃ NO.HCl
259585	-(CH2)2-	H		4-CF3-Ph	HCl	S	C ₁₅ H ₁₈ F ₃ N.HCl
259586	-(CH2)3-	H		2-OH-Ph	HCl	R	C ₁₅ H ₂₁ NO.HCl
259587	-(CH2)3-	H		2-Me-4-benzo-thienyl	HCl		C ₁₈ H ₂₃ NS.HCl
259588	-(CH2)3-	H		3-OH-Ph	HCl	R	C ₁₅ H ₂₁ NO.HCl
259589	-(CH2)3-	H		3-OH-Ph	HCl	S	C ₁₅ H ₂₁ NO.HCl

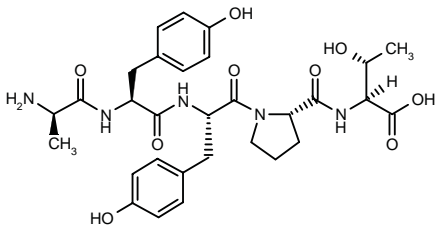
SOURCE – Grünenthal.

REFERENCES

1. Buschmann, H.H. et al. (Grünenthal GmbH) *Dimethyl-(3-aryl-but-3-enyl)amine derivs. with analgesic activity*. EP 799819, JP 98007624.

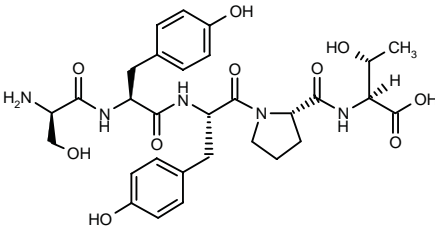
256468

D-Alanyl-L-tyrosyl-L-tyrosyl-L-prolyl-L-threonine



C30-H39-N5-O9; Mol wt: 613.67

ACTION – Analgesic agent with opioid activity, as demonstrated by its ability to induce naloxone-reversible inhibition of electrically evoked contractions in rat vas deferens (IC₅₀ = 1.2 μM). Another related peptide is:



260366: C30-H39-N5-O10

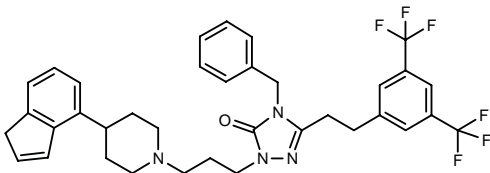
SOURCE – Nisshin Flour Milling.

REFERENCES

1. Yoshikawa, M. and Fukutome, S. (Nisshin Flour Milling Co., Ltd.) *Peptides*. JP 97227590.

259157

4-Benzyl-3-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-1-[3-[4-(1*H*-inden-4-yl)piperidin-1-yl]propyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one



C36-H36-F6-N4-O; Mol wt: 654.70

ACTION – Potent, nonpeptide tachykinin, especially NK₁ receptor, antagonist for the treatment of pain, inflammation, emesis and postherpetic neuralgia; the IC₅₀ value at the NK₁ receptor was < 150 nM.

SOURCE – Merck Sharp & Dohme.

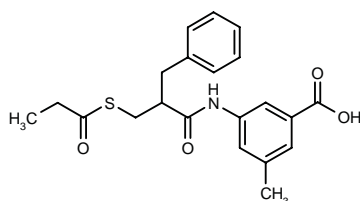
REFERENCES

1. Ladduwahetty, T. and MacLeod, A.M. (Merck Sharp & Dohme, Ltd.) *Triazole derivs. and their use as therapeutic agents*. US 5710161.

BL-2401*

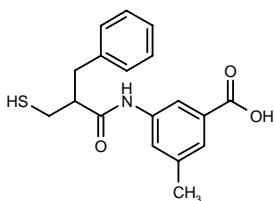
259067

(±)-3-[2-Benzyl-3-(propionylsulfanyl)propionamido]-5-methylbenzoic acid



C21-H23-N-O4-S; Mol wt: 385.48

ACTION – Orally active enkephalinase inhibitor with analgesic and antidepressant-like effects apparently mediated by opioid systems; it dose-dependently (5-100 mg/kg p.o.) inhibited enkephalinase in mice, giving 80.5, 76.6, 67.2 and 48.4% inhibition, respectively, at 1, 2, 4 and 8 h after administration of the highest dose. The compound demonstrated good antinociceptive properties in a range of tests in rodents such as the mouse phenylbenzoquinone writhing test and the rat acetic acid writhing test (ED₅₀ = 12.4 and 55.8 mg/kg p.o., respectively). Antidepressant-like activity was observed in the forced swimming test in mice. The active metabolite **BL-2240** was found to selectively and competitively inhibit enkephalinase activity *in vitro* (IC₅₀ = 5.2 nM using rat striatal enzyme).



BL-2240* [151728]: C18-H19-N-O3-S

SOURCE – Dainippon.

REFERENCES

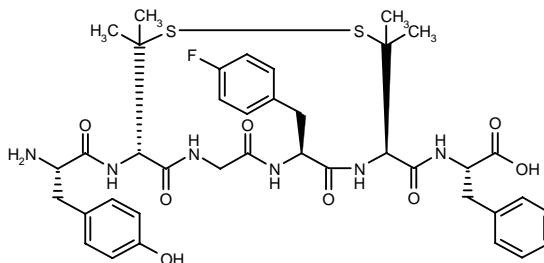
1. Mimura, T. et al. (Dainippon Pharm. Co., Ltd.) *N-Substd. mercaptopropanamide*. AU 8826508, EP 318859, JP 90160760, US 5179125, US 5210266.
2. Kita, A. et al. *Antinociceptive and antidepressant-like profiles on BL-2401, a novel enkephalinase inhibitor, in mice and rats*. Jpn J Pharmacol 1997, 75(4): 337.

*Identified compound **151728** Drug Data Rep 1989, 11(9): 700.

HBP51

257930

L-Tyrosyl-D-penicillaminyglycyl-4-fluoro-L-phenylalanyl-L-penicillaminy-L-phenylalanine cyclic (2→5)-disulfide



C39-H47-F-N6-O8-S2; Mol wt: 810.95

ACTION – Highly potent and selective δ-opioid receptor ligand (IC₅₀ = 0.43 ± 0.08 nM for displacement of [³H]-[p-Cl-Phe⁴]-DPDPE binding in rat brain membranes) with much lower affinity for μ-opioid receptors (IC₅₀ = 1650 ± 210 nM for displacement of [³H]-CTOP binding in rat brain membranes). It exhibited strong potency and selectivity in functional assays inhibiting electrically induced smooth muscle contractions of mouse vas deferens with an IC₅₀ of 0.016 ± 0.005 nM, whereas it showed a much weaker inhibitory effect against electrically induced contractions of guinea pig ileum longitudinal muscle myenteric plexus strips (IC₅₀ = 740 ± 100 nM), giving a selectivity ratio of 45,000.

SOURCE – Univ. Arizona, Tucson, AZ (US).

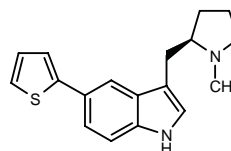
REFERENCES

1. Hruby, V.J. et al. *Cyclic enkephalin analogues with exceptional potency and selectivity for δ-opioid receptors*. J Med Chem 1997, 40(24): 3957.

ANTIMIGRAINE DRUGS

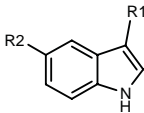
258995

3-[1-Methylpyrrolidin-2(R)-ylmethyl]-5-(2-thienyl)-1H-indole



C18-H20-N2-S; Mol wt: 296.43

ACTION – Antimigraine agent with potent and selective affinity for 5-HT_{1D} receptors (98 and 84% inhibition of [³H]-5-HT binding to 5-HT_{1Dα} [5-HT_{1D}] and 5-HT_{1Dβ} [5-HT_{1B}] receptors, respectively, at 100 nM). Agonist activity was demonstrated by induction of contractions in rabbit saphenous vein (EC₅₀ = 121 nM vs. 220 nM for sumatriptan). Other specifically claimed compounds from this series of thiophene- and furan-tryptamine derivatives include the following:



Compound	R1	R2	Formula
260011	1-Me-2(R)-pyrrolidinyl-CH2	3-thienyl	C ₁₈ H ₂₀ N ₂ S
260012	CH2CH2N(Me)2	3-thienyl	C ₁₆ H ₁₈ N ₂ S
260013	CH2CH2N(Me)2	2-thienyl	C ₁₆ H ₁₈ N ₂ S
260014	CH2CH2N(Me)2	5-(CH2OH)-2-thienyl	C ₁₇ H ₂₀ N ₂ OS
260015	1-Me-2(S)-pyrrolidinyl-CH2	2-thienyl	C ₁₈ H ₂₀ N ₂ S
260016	CH2CH2NH2	2-thienyl	C ₁₄ H ₁₄ N ₂ S
260017	1-Me-3-pyrrolidinyl	2-thienyl	C ₁₇ H ₁₈ N ₂ S
260018	CH2CH2N(Me)2	5-Cl-2-thienyl	C ₁₆ H ₁₇ ClN ₂ S
260019	CH(OH)CH2N(Me)2	3-thienyl	C ₁₈ H ₁₈ N ₂ OS
260021	2-pyrrolidinyl-CH2CH2	2-thienyl	C ₁₈ H ₂₀ N ₂ S
260022	CH2CH2N(Me)2	5-Me-2-thienyl	C ₁₇ H ₂₀ N ₂ S
260023	1-Me-3-pyrrolidinyl-CH2CH2	3-thienyl	C ₁₉ H ₂₂ N ₂ S
260024	CH2CH2N(Et)2	2-thienyl	C ₁₈ H ₂₂ N ₂ S

SOURCE – Allelix.

REFERENCES

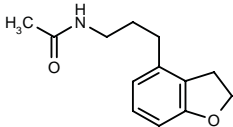
1. Meng, Q. et al. (Allelix Biopharm., Inc.) *Thiophene- and furan-tryptamine derivs.* WO 9743281.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

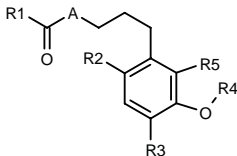
258988

N-[3-(2,3-Dihydrobenzofuran-4-yl)propyl]acetamide



C13-H17-N-O2; Mol wt: 219.28

ACTION – Agent for the treatment of chronobiological disorders, especially in the elderly, with high affinity and selectivity for melatonin receptors and agonist or antagonist activity against human melatonin MEL₁ receptors expressed in CHO cells. Also claimed for use in the treatment of glaucoma, cancer, psychiatric disorders, neurodegenerative disorders and neuroendocrine disorders. Other specifically claimed benzofurans and benzopyrans include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
259344	cyclopropyl	H	H	-(CH2)2-	NH		C ₁₅ H ₁₉ NO ₂
259345	cyclopropyl	Cl	H	-(CH2)2-	NH		C ₁₅ H ₁₈ ClNO ₂
259346	cyclopropyl	Cl	F	-(CH2)2-	NH		C ₁₅ H ₁₇ ClFNO ₂
259347	cyclopropyl	Cl	F	-CH=CH-	NH		C ₁₅ H ₁₅ ClFNO ₂
259348	cyclopropyl	H	H	-CH=CH-	NH		C ₁₅ H ₁₇ NO ₂
259349	cyclopropyl	H	H	-(CH2)3-	NH		C ₁₆ H ₂₁ NO ₂
259350	Me	F	H	-CH=CH-	NH		C ₁₃ H ₁₄ FNO ₂
259351	cyclopropyl	F	H	-(CH2)2-	O		C ₁₅ H ₁₇ FO ₃

SOURCE – Glaxo Wellcome.

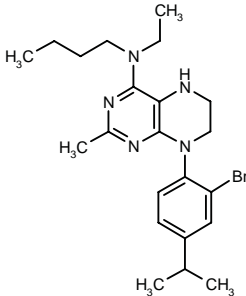
REFERENCES

1. Ellis, F. et al. (Glaxo Group, Ltd.) *Benzofurans and benzopyrans as chronobiological agents.* WO 9743272.

ANXIOLYTICS

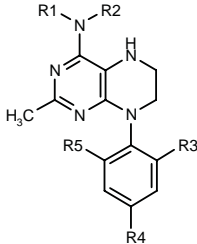
259028

8-(2-Bromo-4-isopropylphenyl)-4-(N-butyl-N-ethylamino)-2-methyl-5,6,7,8-tetrahydropteridine

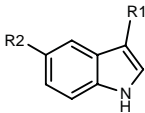


C22-H32-Br-N5; Mol wt: 446.43

ACTION – Anxiolytic agent and antidepressant, a corticotropin-releasing factor (CRF) antagonist, from a series of tetrahydropteridines and pyridylpiperazines, wherein the following are also specifically claimed:



Compound	R1	R2	R3	R4=R5	Formula
260209	Et	Bu	Cl	OMe	C ₂₁ H ₃₀ ClN ₅ O ₂
260210	Et	Bu	Me	Me	C ₂₂ H ₃₃ N ₅
260211	CH(Et)CH2OMe	H	Me	Me	C ₂₁ H ₃₁ N ₅ O



Compound	R1	R2	Formula
260011	1-Me-2(R)-pyrrolidinyl-CH2	3-thienyl	C ₁₈ H ₂₀ N ₂ S
260012	CH2CH2N(Me)2	3-thienyl	C ₁₆ H ₁₈ N ₂ S
260013	CH2CH2N(Me)2	2-thienyl	C ₁₆ H ₁₈ N ₂ S
260014	CH2CH2N(Me)2	5-(CH2OH)-2-thienyl	C ₁₇ H ₂₀ N ₂ OS
260015	1-Me-2(S)-pyrrolidinyl-CH2	2-thienyl	C ₁₈ H ₂₀ N ₂ S
260016	CH2CH2NH2	2-thienyl	C ₁₄ H ₁₄ N ₂ S
260017	1-Me-3-pyrrolidinyl	2-thienyl	C ₁₇ H ₁₈ N ₂ S
260018	CH2CH2N(Me)2	5-Cl-2-thienyl	C ₁₆ H ₁₇ ClN ₂ S
260019	CH(OH)CH2N(Me)2	3-thienyl	C ₁₈ H ₁₈ N ₂ OS
260021	2-pyrrolidinyl-CH2CH2	2-thienyl	C ₁₈ H ₂₀ N ₂ S
260022	CH2CH2N(Me)2	5-Me-2-thienyl	C ₁₇ H ₂₀ N ₂ S
260023	1-Me-3-pyrrolidinyl-CH2CH2	3-thienyl	C ₁₉ H ₂₂ N ₂ S
260024	CH2CH2N(Et)2	2-thienyl	C ₁₈ H ₂₂ N ₂ S

SOURCE – Allelix.

REFERENCES

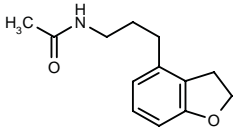
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

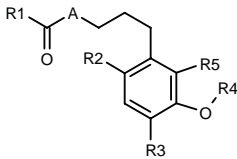
258988

N-[3-(2,3-Dihydrobenzofuran-4-yl)propyl]acetamide



C13-H17-N-O2; Mol wt: 219.28

ACTION – Agent for the treatment of chronobiological disorders, especially in the elderly, with high affinity and selectivity for melatonin receptors and agonist or antagonist activity against human melatonin MEL₁ receptors expressed in CHO cells. Also claimed for use in the treatment of glaucoma, cancer, psychiatric disorders, neurodegenerative disorders and neuroendocrine disorders. Other specifically claimed benzofurans and benzopyrans include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
259344	cyclopropyl	H	H	-(CH2)2-	NH		C ₁₅ H ₁₉ NO ₂
259345	cyclopropyl	Cl	H	-(CH2)2-	NH		C ₁₅ H ₁₈ ClNO ₂
259346	cyclopropyl	Cl	F	-(CH2)2-	NH		C ₁₅ H ₁₇ ClFNO ₂
259347	cyclopropyl	Cl	F	-CH=CH-	NH		C ₁₅ H ₁₅ ClFNO ₂
259348	cyclopropyl	H	H	-CH=CH-	NH		C ₁₅ H ₁₇ NO ₂
259349	cyclopropyl	H	H	-(CH2)3-	NH		C ₁₆ H ₂₁ NO ₂
259350	Me	F	H	-CH=CH-	NH		C ₁₃ H ₁₄ FNO ₂
259351	cyclopropyl	F	H	-(CH2)2-	O		C ₁₅ H ₁₇ FO ₃

SOURCE – Glaxo Wellcome.

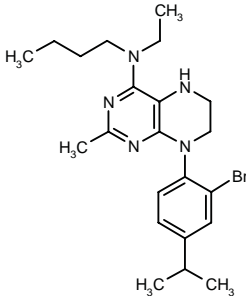
REFERENCES

1. Ellis, F. et al. (Glaxo Group, Ltd.) *Benzofurans and benzopyrans as chronobiological agents.* WO 9743272.

ANXIOLYTICS

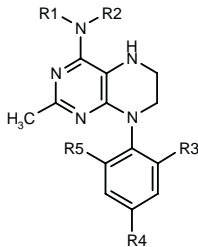
259028

8-(2-Bromo-4-isopropylphenyl)-4-(N-butyl-N-ethylamino)-2-methyl-5,6,7,8-tetrahydropteridine



C22-H32-Br-N5; Mol wt: 446.43

ACTION – Anxiolytic agent and antidepressant, a corticotropin-releasing factor (CRF) antagonist, from a series of tetrahydropteridines and pyridylpiperazines, wherein the following are also specifically claimed:



Compound	R1	R2	R3	R4=R5	Formula
260209	Et	Bu	Cl	OMe	C ₂₁ H ₃₀ ClN ₅ O ₂
260210	Et	Bu	Me	Me	C ₂₂ H ₃₃ N ₅
260211	CH(Et)CH2OMe	H	Me	Me	C ₂₁ H ₃₁ N ₅ O

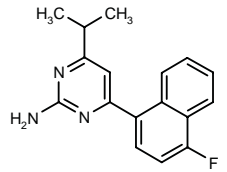
SOURCE – DuPont Merck.

REFERENCES

1. Wilde, R.G. (The Du Pont Merck Pharm. Co.) *Tetrahydropteridines and pyridylpiperazines for treatment of neurological disorders*. WO 9744038.

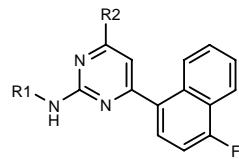
259044

4-(4-Fluoro-1-naphthyl)-6-isopropylpyrimidin-2-amine

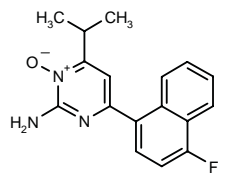


C17-H16-F-N3; Mol wt: 281.33

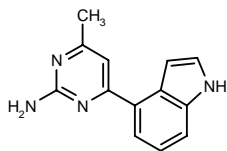
ACTION – Anxiolytic agent, a selective 5-HT_{2B} antagonist also potentially useful in the treatment of panic disorder, obsessive–compulsive disorder, alcoholism, depression, migraine, hypertension, sleep disorders, anorexia nervosa and priapism. Other specifically claimed arylpyrimidine derivatives include the following:



Compound	R1	R2	Formula
260219	H	CF(Me)2	C ₁₇ H ₁₅ F ₂ N ₃
260220	H	CH(Me)2OH	C ₁₇ H ₁₆ FN ₃ O
260221	H	CF(Me)2	C ₁₇ H ₁₄ F ₃ N ₃
260222	Me	i-Pr	C ₁₈ H ₁₈ FN ₃
260223	H	i-Bu	C ₁₈ H ₁₈ FN ₃
260224	H	t-Bu	C ₁₈ H ₁₈ FN ₃



260218: C17-H16-F-N3-O



260225: C13-H12-N4

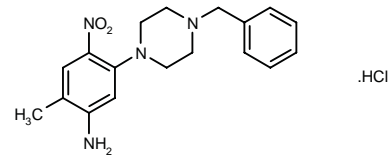
SOURCE – Roche.

REFERENCES

1. Berger, J. et al. (F. Hoffmann-La Roche AG) *Aryl pyrimidine derivs*. WO 9744326.

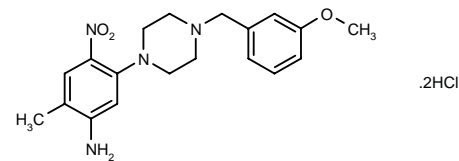
259047

5-(4-Benzylpiperazin-1-yl)-2-methyl-4-nitroaniline hydrochloride



C18-H22-N4-O2.HCl; Mol wt: 362.86

ACTION – Agent for the treatment of CNS disorders such as anxiety, depression and migraine with high affinity for 5-HT_{2C} (K_i = 48.0 nM against [³H]-mesulergine binding in pig brain choroid plexus membrane preparations) and σ₁-receptors (K_i = 6.0 nM against [³H]-(+)-pentazocine binding in rat brain cerebellar membrane preparations). Compound inhibited 5-HT-induced contractions of rat stomach fundus smooth muscle preparations with an IC₅₀ value of 3.3 nM. In addition, it was found to exhibit oral antiulcer activity in animal models following p.o. administration. Another compound from this series of piperazine and homopiperazine derivatives is:



260267: C19-H24-N4-O3.2HCl

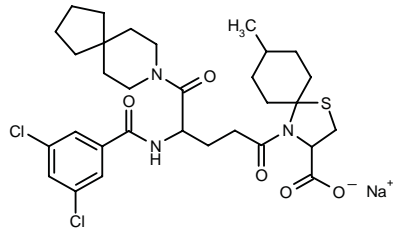
SOURCE – Egis.

REFERENCES

1. Rátné Simonek, I. et al. (Egis Gyógyszergyár RT) *Novel piperazine or homopiperazine derivs., pharmaceutical compsns. containing the same and a process for their preparation*. WO 9744334.

259051

4-[5-(8-Azaspiro[4.5]dec-8-yl)-4-(3,5-dichlorobenzamido)-5-oxopentanoyl]-8-methyl-1-thia-4-azaspiro[4.5]decane-3-carboxylic acid sodium salt



C31-H40-Cl2-Na-N3-O5-S; Mol wt: 660.64

ACTION – Anxiolytic and gastric antisecretory agent, a selective antagonist of cholecystokinin CCK_B/gastrin receptors in the CNS (IC₅₀ = 60 nM against [³H]-[N-methyl-N-leucine]-CCK-8 binding in guinea pig cortex vs. IC₅₀ = 3 nM for pentagastrin) and in the gastrointestinal system (IC₅₀ = 3 nM for inhibition of the increase in cytosolic calcium induced by gastrin in rabbit gastric mucosa cells, with no affinity for CCK_A receptors (IC₅₀ > 10 μM against CCK-8-induced guinea pig gallbladder contractions). Anxiolytic activity was demonstrated in an elevated plus-maze in rats.

SOURCE – Rotta Research.

REFERENCES

1. Makovec, F. et al. (Rotta Res. Lab. SpA) *Cyclic polyamides of glutamic acid and aspartic acid with anti-gastrin activity, a method for their preparation and their pharmaceutical use.* WO 9744341.

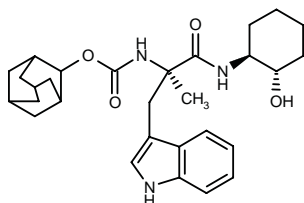
CI-1015*

228802

2(R)-(2-Adamantyloxycarbonylamino)-N-[2(S)-hydroxy-1(S)-cyclohexyl]-3-(3-indolyl)-2-methylpropionamide

[1S-[1 α (S*),2 β]]-N-[2-(2-Hydroxycyclohexyl-1-ylamino)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamic acid 2-adamantyl ester

PD-145942



C29-H39-N3-O4; Mol wt: 493.64

ACTION – Cholecystokinin CCK_B receptor antagonist with good oral bioavailability and the ability to cross the blood–brain barrier. CI-1015 binds selectively to CCK_B receptors (IC₅₀ = 3.0 nM) with respect to CCK_A receptors (IC₅₀ = 2900 nM). It exhibited anxiolytic-like properties in animal models of anxiety. CI-1015 has been chosen as a development candidate due to its improved pharmacokinetic and activity profile compared to the parent compound CI-988.

SOURCE – Warner-Lambert.

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2. Horwell, D.C. et al. (Warner-Lambert Co.) *Indole derivs. as CCK receptor antagonists.* EP 749422, JP 97510440, WO 9524389.
3. Boden, P.R. et al. *Evaluation of a series of novel CCKB antagonists using a functional assay in the rat central nervous system.* Brit J Pharmacol 1994, 112(2): 666.
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5. Suman-Chauhan, N. et al. *The influence of guanyl nucleotide on agonist and antagonist affinity at guinea-pig CCK-B/gastrin receptors: Binding studies using [3H]PD140376.* Regul Peptides 1996, 65(1): 37.
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7. Trivedi, B.K. et al. *Second generation "peptoid" CCK-B receptor antagonists: Identification and development of N-(adamantyloxycarbonyl)-alpha-methyl-(R)-tryptophan derivative (CI-1015) with an improved pharmacokinetic profile.* J Med Chem 1998, 41(1): 38.
8. Wang, Y.-M.C. et al. *Pharmacokinetics and bioavailability of PD 145942 in cynomolgus monkeys.* Pharm Res 1995, 12(9, Suppl.): Abst PPDM 8397.

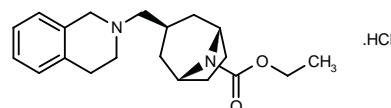
9. *The right stuff. A full portfolio of innovative products that addresses the needs of patients. The patient is waiting.* Oppenheimer & Co. 7th Annu Healthcare Conf (Oct 28-29, New York) 1996.

*Identified compound **228802** Drug Data Rep 1996, 18(2): 115.

ANTIPSYCHOTIC DRUGS

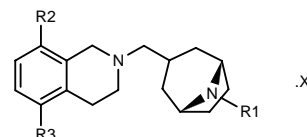
257256

exo-3-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)-8-azabicyclo[3.2.1]octane-8-carboxylic acid ethyl ester hydrochloride



C20-H28-N2-O2.HCl; Mol wt: 364.91

ACTION – Antipsychotic agent from a series of compounds having strong affinity for dopamine D₃ and D₂ receptors and 5-HT_{1A} and 5-HT₂ receptors, or strong and selective affinity for D₃ receptors relative to the other receptor types. The compound is reported to inhibit amphetamine-induced hyperactivity in rats and to have weak cataleptogenic activity. Within this series of 3-[(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl]-8-azabicyclo[3.2.1]octane derivatives, the following are also included:



Compound	R1	R2	R3	X	Isomer	Formula
259590	CO ₂ Et	OMe	OMe	HCl	exo	C ₂₂ H ₃₂ N ₂ O ₄ .HCl
259591	CO ₂ Et	OMe	OMe	HCl	endo	C ₂₂ H ₃₂ N ₂ O ₄ .HCl
259592	4-Me-PhCH ₂	H	i-PrO	fumarate	exo	C ₂₈ H ₃₈ N ₂ O ₄ .C ₄ H ₄ O ₄
259593	COPh	H	H	HCl	exo	C ₂₄ H ₂₈ N ₂ O ₄ .HCl
259594	CH ₂ Ph	H	i-PrO	fumarate	exo	C ₂₇ H ₃₆ N ₂ O ₄ .C ₄ H ₄ O ₄
259595	CH ₂ Ph	H	OMe	fumarate	exo	C ₂₅ H ₃₂ N ₂ O ₄ .C ₄ H ₄ O ₄
259596	4-Me-PhCO	H	OMe	HCl	exo	C ₂₆ H ₃₂ N ₂ O ₂ .HCl
259597	COPh	OMe	OMe	HCl	exo	C ₂₆ H ₃₂ N ₂ O ₃ .HCl
259598	CH ₂ Ph	OMe	OMe	HCl	exo	C ₂₆ H ₃₄ N ₂ O ₂ .HCl
259599	3,4-(Cl)2-PhCO	OMe	OMe	HCl	exo	C ₂₆ H ₃₀ Cl ₂ N ₂ O ₃ .HCl
259600	4-Me-PhCH ₂	H	OMe	fumarate	exo	C ₂₆ H ₃₄ N ₂ O ₄ .C ₄ H ₄ O ₄
259601	3-EtO-PhCO	OMe	OMe	HCl	exo	C ₂₈ H ₃₆ N ₂ O ₄ .HCl
259602	3-EtO-PhCO	OMe	OMe	HCl	endo	C ₂₈ H ₃₆ N ₂ O ₄ .HCl

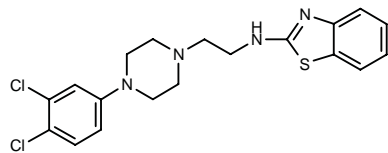
SOURCE – Synthélabo.

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1. Sevrin, M. et al. (Synthélabo) *3-[(1,2,3,4-Tetrahydroisoquinoline-2-yl)methyl]-8-azabicyclo[3.2.1]octane derivs., their preparation and their application in therapeutics.* FR 2747386, WO 9738998.

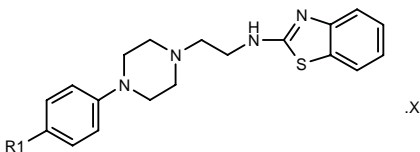
258987

N-(Benzothiazol-2-yl)-*N*-[2-[4-(3,4-dichlorophenyl)-piperazin-1-yl]ethyl]amine



C19-H20-Cl2-N4-S; Mol wt: 407.36

ACTION – Antipsychotic agent a potent and selective dopamine D₄ antagonist (pIC₅₀ = 7 or greater against [³H]-spiperone binding to cloned human D₄ receptors expressed in CHO cells). Other compounds from this series of specifically claimed alkylaminobenzothiazole and -benzoxazole derivatives include the following:



Compound	R1	X	Formula
259365	H		C ₁₉ H ₂₂ N ₄ S
259366	Cl		C ₁₉ H ₂₁ ClN ₄ S
259367	Br	fumarate	C ₁₉ H ₂₁ BrN ₄ S.C ₄ H ₄ O ₄

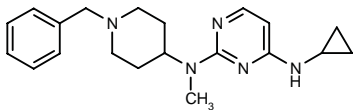
SOURCE – Janssen.

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1. Kennis, L.E.J. et al. (Janssen Pharm. NV) *Alkylaminobenzothiazole and -benzoxazole derivs.* WO 9743271.

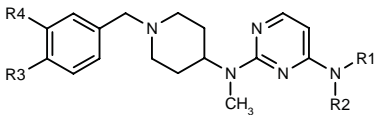
258993

*N*²-(1-Benzylpiperidin-4-yl)-*N*⁴-cyclopropyl-*N*²-methylpyrimidine-2,4-diamine



C20-H27-N5; Mol wt: 337.47

ACTION – Antipsychotic agent with potent and selective dopamine D₄ receptor-antagonist activity (pIC₅₀ = 7 or more against [³H]-spiperone binding to cloned human D₄ receptors expressed in CHO cells). Other specifically claimed compounds from this series of 2,4-diamino-pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
259452	H	Et	-OCH2O-		C ₂₀ H ₂₇ N ₅ O ₂
259453	H	cyclopropyl	-OCH2O-		C ₂₁ H ₂₇ N ₅ O ₂
259454	Me	Me	Cl	H	C ₁₉ H ₂₆ ClN ₅

Compound	R1	R2	R3	R4	Formula
259455	Me	Me	H	F	C ₁₉ H ₂₆ FN ₅
259456	Me	Me	CF3	H	C ₂₀ H ₂₆ F ₃ N ₅
259457	Me	Me	Me	H	C ₂₀ H ₂₉ N ₅
259458	Me	Me	H	Me	C ₂₀ H ₂₉ N ₅

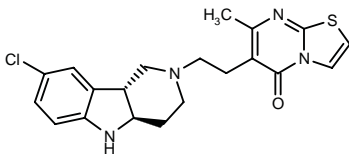
SOURCE – Janssen.

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1. Bosmans, J.-P.R.M.A. et al. (Janssen Pharm. NV) *2,4-Diaminopyrimidine derivatives as dopamine D4 receptor antagonists.* WO 9743279.

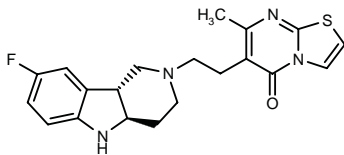
259029

trans-6-[2-(8-Chloro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indol-2-yl)ethyl]-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one

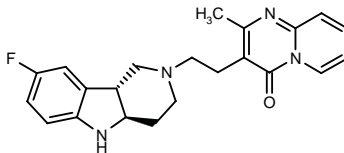


C20-H21-Cl-N4-O-S; Mol wt: 400.93

ACTION – Antipsychotic agent with central dopamine- and 5-HT-antagonist activity and lacking significant α -adrenoceptor-antagonist activity in the norepinephrine test, suggesting the absence of hypotensive activity. Pharmacological activity was demonstrated in the combined apomorphine (APO), tryptamine (TRY) and norepinephrine (NOR) test in rats, the ED₅₀ values being 0.03 mg/kg p.o. (APO), 0.02 mg/kg p.o. (TRY convulsions), 0.005 mg/kg p.o. (TRY hyperemia) and > 10 mg/kg p.o. (NOR). Other specifically claimed hexahydropyrido[4,3-*b*]indole derivatives include the following:



260207: C20-H21-F-N4-O-S



260208: C22-H23-F-N4-O

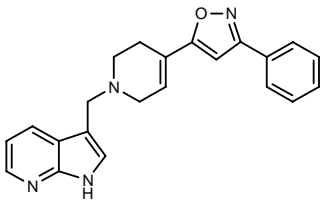
SOURCE – Janssen.

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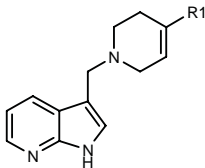
259394

3-[4-(3-Phenylisoxazol-5-yl)-1,2,3,6-tetrahydropyridin-1-ylmethyl]pyrrolo[2,3-*b*]pyridine



C22-H20-N4-O; Mol wt: 356.43

ACTION – Antipsychotic agent that selectively binds to dopamine D₄ receptors (K_i < 1.5 μM against [³H]-spiperone binding to human D₄ receptors expressed in clonal cell lines), reported to possess enhanced metabolic stability over structurally related compounds. A representative compound from a series of specifically claimed pyrrolo[2,3-*b*]pyridine derivatives, wherein the following are also included:



Compound	R1	Formula
259550	3-(3-Pyr)-5-isoxazolyl	C ₂₁ H ₁₉ N ₅ O
259551	3-(4-Cl-Ph)-5-isoxazolyl	C ₂₂ H ₁₉ ClN ₄ O
259552	1-Ph-1,2,3-triazol-4-yl	C ₂₁ H ₂₀ N ₆
259553	3-Ph-Ph	C ₂₈ H ₂₃ N ₃
259554	4-Ph-Ph	C ₂₈ H ₂₃ N ₃
259555	3-Ph-1,2,4-oxadiazol-5-yl	C ₂₁ H ₁₉ N ₅ O
259556	5-Ph-2-oxazolyl	C ₂₂ H ₂₀ N ₄ O
259557	5-Ph-2-thienyl	C ₂₃ H ₂₁ N ₃ S
259558	trans-2-Ph-cyclopropyl	C ₂₂ H ₂₃ N ₃

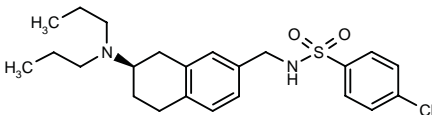
SOURCE – Merck Sharp & Dohme.

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1. Curtis, N.R. et al. (Merck Sharp & Dohme, Ltd.) *Pyrrolo-pyridine derivs.* US 5712285.

259895

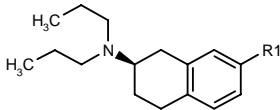
4-Chloro-*N*-[7(*R*)-(dipropylamino)-5,6,7,8-tetrahydronaphthalen-2-ylmethyl]benzenesulfonamide



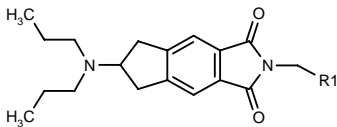
C23-H31-Cl-N2-O2-S; Mol wt: 435.02

ACTION – Agent for the treatment of CNS disorders such as schizophrenia, mania, depression, anxiety, obsessive-compulsive disorder, drug addiction, Parkinson's disease, dementia, sleep disorders and circadian rhythm disorders with high affinity for dopamine D₃ receptors (K_i = 12 nM against [³H]-spiperone binding to rat D₃ receptors expressed in CHO-K1 cells) and selectivity relative to D₂ receptors (K_i = 206 nM against [³H]-(*R*)-5-(dipropylamino)-

5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one binding to rat D₂ receptors expressed in CHO-K1 cells). Other related compounds include the following:



Compound	R1	Formula
260471	4-CN-PhSO2NHCH2	C ₂₄ H ₃₁ N ₃ O ₂ S
260472	4-NO2-PhSO2NHCH2	C ₂₃ H ₃₁ N ₃ O ₄ S
260473	3-CN-PhSO2NHCH2	C ₂₄ H ₃₁ N ₃ O ₂ S
260474	1-Me-4-imidazolyl-SO2NHCH2	C ₂₁ H ₃₂ N ₄ O ₂ S
260475	4-Cl-PhCONHCH2	C ₂₄ H ₃₁ ClN ₂ O
260476	4-Cl-PhSO2NH	C ₂₂ H ₂₉ ClN ₂ O ₂ S
260477	4-CN-Ph-SO2NH	C ₂₃ H ₂₉ N ₃ O ₂ S



Compound	R1	Formula
260478	2-Me-5-thiazolyl	C ₂₂ H ₂₇ N ₃ O ₂ S
260479	1,2,4-oxadiazol-3-yl	C ₂₀ H ₂₄ N ₄ O ₃

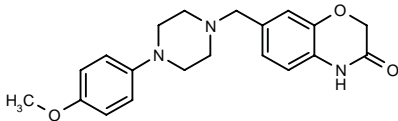
SOURCE – Pharmacia & Upjohn.

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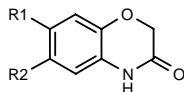
259904

7-[4-(4-Methoxyphenyl)piperazin-1-ylmethyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-one



C20-H23-N3-O3; Mol wt: 353.42

ACTION – Antipsychotic agent, a potent and selective dopamine D₄ receptor antagonist (K_i = 5.0 nM) with > 1000-fold selectivity over dopamine D₂ receptors (K_i = 5882.4 nM). Other compounds from this series of specifically claimed benzoxazinones include the following:



Compound	R1	R2	Formula
260457	H	4-[3,4-(Me)2-Ph]-1-Piz-CH2	C ₂₁ H ₂₅ N ₃ O ₂
260458	H	4-(5-Me-2-Pyr)-1-Piz-CH2	C ₁₉ H ₂₂ N ₄ O ₂
260459	H	4-[4,5-(Me)2-thiazolyl]-1-Piz-CH2	C ₁₈ H ₂₂ N ₄ O ₂ S
260460	H	4-(4-MeO-Ph)-1-Piz-CH2	C ₂₀ H ₂₃ N ₃ O ₃
260461	4-(5-Me-2-Pyr)-1-Piz-CH2	H	C ₁₉ H ₂₂ N ₄ O ₂

SOURCE – Warner-Lambert.

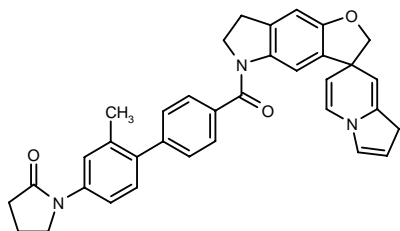
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ANTIDEPRESSANTS

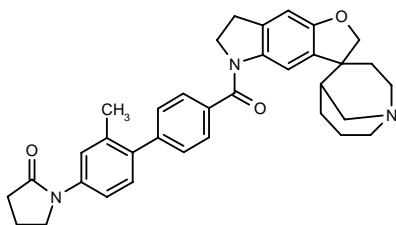
257767

1-[2-Methyl-4'-[3,5,6,7-tetrahydro-2*H*-spiro[furo[2,3-*f*]indole-3,7'-indolizin]-5-ylcarbonyl]biphenyl-4-yl]pyrrolidin-2-one

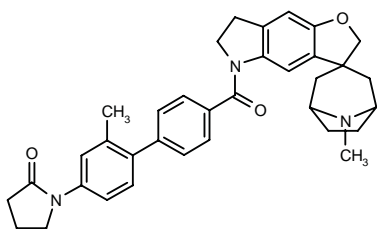


C35-H31-N3-O3; Mol wt: 541.65

ACTION – Antidepressant with 5-HT_{1B} (formerly 5-HT_{1Dβ}) receptor-antagonist activity, also claimed for the treatment of other CNS disorders including anxiety. Other specifically claimed spiroazabicyclic compounds include the following:



259142: C35-H37-N3-O3



259143: C35-H37-N3-O3

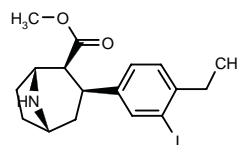
SOURCE – SmithKline Beecham.

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1. Gaster, L.M. (SmithKline Beecham plccd.) *Spiroazabicyclic cpds., processes for their preparation, and their pharmaceutical use*. WO 9741125.

257922

[1*R*-(*exo,exo*)]-3-(4-Ethyl-3-iodophenyl)-8-azabicyclo-[3.2.1]octan-2-ylcarboxylic acid methyl ester



C17-H22-I-N-O2; Mol wt: 399.27

Tartrate salt, m.p. 160-1 °C, [α]_D²⁵ -56.9° (c 0.26, MeOH).

ACTION – Selective, high-affinity ligand for the 5-HT transporter, a cocaine/Win-35065-2 analog with high affinity for the 5-HT transporter (IC₅₀ = 0.69 ± 0.07 nM for displacement of [³H]-paroxetine binding) and relatively low affinity for both dopamine and norepinephrine transporters (IC₅₀ = 329 ± 13 and 148 ± 9.2 nM, respectively, for displacement of [³H]-Win-35428 and [³H]-nisoxetine binding). The selectivity of the compound was also demonstrated in competition binding studies in mice using [¹²⁵I]-RTI-55 as the ligand (with affinity for both 5-HT and dopamine transporters), which revealed that the compound shows similar ED₅₀s and brain distribution to fluoxetine and sertraline. Potentially useful as an antidepressant and the iodine-123 analog may be useful as a SPECT ligand for studying this transporter in the brain.

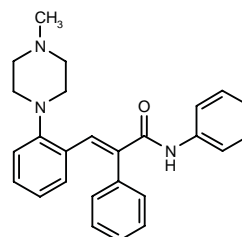
SOURCES – Johns Hopkins Univ. School Med., Baltimore, MD (US); Natl. Inst. Drug Abuse (NIDA), Baltimore, MD (US); Research Triangle Inst., Research Triangle Park, NC (US).

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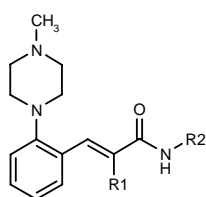
258713

3-[2-(4-Methylpiperazin-1-yl)phenyl]-*N*,2-diphenyl-2-propenamide



C26-H27-N3-O; Mol wt: 397.52

ACTION – Psychotherapeutic agent from a series of potent agonists and/or antagonists of 5-HT_{1A} and/or 5-HT_{1D} receptors (IC₅₀ < 0.60 μM for 5-HT_{1D} and < 1.0 μM for 5-HT_{1A} receptors), potentially useful for the treatment of disorders such as depression, anxiety, obsessive-compulsive and panic disorders, premature ejaculation, hypertension, eating disorders, migraine, Alzheimer's disease and Parkinson's disease. Other specifically claimed arylacrylamide derivatives include the following:



Compound	R1	R2	Formula
259129	H	4-CF ₃ -Ph	C ₂₁ H ₂₂ F ₃ N ₃ O
259130	H	3,4-(Cl)2-Ph	C ₂₀ H ₂₁ Cl ₂ N ₃ O
259131	Ph	4-Cl-PhCH ₂	C ₂₇ H ₂₈ ClN ₃ O
259132	H	4-Cl-PhCH ₂	C ₂₁ H ₂₄ ClN ₃ O

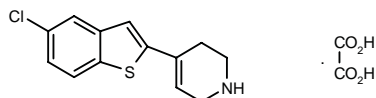
SOURCE – Pfizer.

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- Howard, H.R. and Segelstein, B.E. (Pfizer, Inc.) *Arylacrylamide derivs. as 5HT₁ agonists or antagonists*. EP 810220.

258727

5-Chloro-2-(1,2,3,6-tetrahydropyridin-4-yl)benzo[*b*]-thiophene oxalate



C₁₃H₁₂Cl-N-S.C₂H₂O₄; Mol wt: 339.79

ACTION – Antidepressant, an inhibitor of 5-HT reuptake from a series of tetrahydropyridinyl- and piperidyl-indoles and benzothiophenes.

SOURCE – Lilly.

REFERENCES

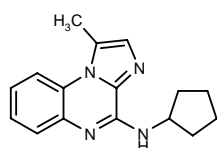
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IRFI-165*

252427

N-Cyclopentyl-*N*-(1-methylimidazo[1,2-*a*]quinoxalin-4-yl)amine

4-(Cyclopentylamino)-1-methylimidazo[1,2-*a*]quinoxaline



C₁₆H₁₈N₄; Mol wt: 266.35

ACTION – Potent and selective, centrally active, nonxanthine adenosine A₁ receptor antagonist ($K_i = 7.9$ nM for displacement of [³H]-DPCPX binding in rat brain synaptosomal membranes; $K_i A_{2a}/K_i A_1 = 300$) chosen for further evaluation. It exhibited antidepressant-like properties in animal models such as the forced swimming test in rats (doses of 0.01 mg/kg i.p. and above).

SOURCE – Biomedica Foscama.

REFERENCES

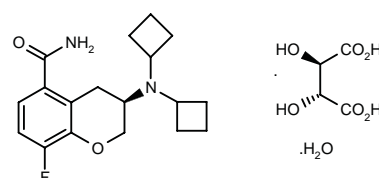
- Ceccarelli, S. et al. (Biomed. Foscama Ind. Chim.-Farm. SpA) *Imidazo[1,2-*a*]quinoxalin-4-amines active as adenosine antagonists, process for their preparation and pharmaceutical compsns. thereof*. WO 9719079.
- Ceccarelli, S. et al. *Imidazo[1,2-*a*]quinoxalin-4-amines: A novel class of centrally active nonxanthine A1-adenosine receptor antagonists*. 1st Ital Swiss Meet Med Chem (Sept 23-26, Torino) 1997, 45.

*Identified compound **252427** Drug Data Rep 1997, 19(9): 782.

NAD-299

230573

3(*R*)-(N,N-Dicyclobutylamino)-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide (*R,R*)-hydrogentartrate hydrate



C₁₈H₂₃F-N₂O₂.C₄H₆O₆.H₂O; Mol wt: 486.49

ACTION – Potent and selective 5-HT_{1A} antagonist that shows high affinity for the 5-HT_{1A} receptor ($K_i = 0.59 \pm 0.08$ nM for inhibition of [³H]-8-OH-DPAT binding in rat hippocampus) and some affinity for α_1 - and β -adrenoceptors ($K_i = 260$ and 340 nM, respectively, for inhibition of [³H]-prazosin and [³H]-DHA binding in rat cortex). Functional antagonist activity at 5-HT_{1A} receptors was demonstrated by blockade of 5-HT-induced inhibition of vasoactive intestinal peptide (VIP)-stimulated cAMP production in GH₄ZD10 cells ($K_B = 1$ nM), as well as by inhibition of 8-OH-DPAT-induced responses in rats, effective doses being in the range of 0.03-0.35 μ mol/kg s.c. NAD-299 is currently undergoing phase I clinical trials for depression and anxiety.

SOURCE – Astra Arcus.

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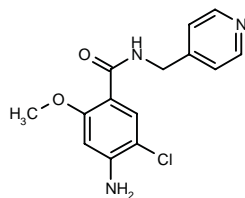
- Evenden, J.L. et al. (Astra AB) *Novel (R)-5-carbamoyl-8-fluoro-3-,N,N-disubst.-amino-3,4-dihydro-2H-1-benzopyranes*. EP 725779, JP 97504287, WO 9511891.
- Evenden, J. and Thorberg, S.-O. (Astra AB) *A combination of a 5-HT uptake inhibitor with a selective 5-HT1A antagonist*. WO 9633710.
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- Johansson, L. et al. *The pharmacological characterization of a novel selective 5-hydroxytryptamine1A receptor antagonist, NAD-299*. J Pharmacol Exp Ther 1997, 283(1): 216.
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

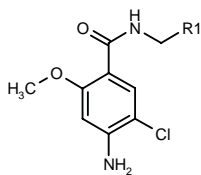
258984

4-Amino-5-chloro-2-methoxy-*N*-(4-pyridylmethyl)-benzamide



C14-H14-Cl-N3-O2; Mol wt: 291.74

ACTION – Anticonvulsant giving an ED₅₀ < 10 mg/kg i.p. in the maximal electroshock test in mice; compound also proved effective in protecting mice against pentylenetetrazol-induced seizures at 50 mg/kg i.p. Other compounds from this series of benzamide derivatives include the following:



Compound	R1	Formula
259494	3-Pyr	C ₁₄ H ₁₄ ClN ₃ O ₂
259495	2-Pyr	C ₁₄ H ₁₄ ClN ₃ O ₂

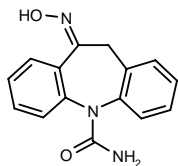
SOURCE – Bristol-Myers Squibb.

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259902

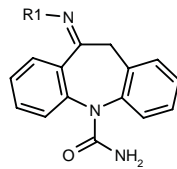
10-(Hydroxyimino)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide



C15-H13-N3-O2; Mol wt: 267.29

ACTION – Agent for the treatment of central and peripheral nervous system disorders such as epilepsy, trigeminal neuralgia and affective disorders, a derivative of oxcarbazepine proven to exhibit greater or similar anticonvulsant activity compared to oxcarbazepine and carba-

mazepine in the maximal electroshock (MES) and metrazol seizure tests in rats. Other specifically claimed compounds include the following:



Compound	R1	Formula
260450	OAc	C ₁₇ H ₁₅ N ₃ O ₃
260451	OMe	C ₁₆ H ₁₅ N ₃ O ₂
260453	OCO2Et	C ₁₈ H ₁₇ N ₃ O ₄
260454	NHPh	C ₂₁ H ₁₈ N ₄ O
260455	NHCONH2	C ₁₆ H ₁₅ N ₅ O ₂
260456	(CH2)3CO2Me	C ₂₀ H ₂₁ N ₃ O ₃

SOURCE – Portela

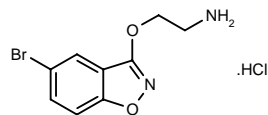
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1. Benes, J. et al. (Portela & Ca. SA) *New derivs. of 10,11-dihydro-10-oxo-5H-dibenz[*b,f*]azepine-5-carboxamide.* WO 9745416.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

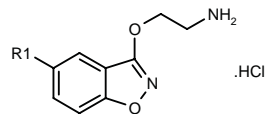
256432

3-(2-Aminoethoxy)-5-bromo-1,2-benzisoxazole hydrochloride



C9-H9-Br-N2-O2.HCl; Mol wt: 293.55

ACTION – Potent inhibitor of monoamine oxidase B (MAO-B; IC₅₀ = 0.32 nM) with 4500-55,000-fold selectivity over MAO-A and reported to exhibit low toxicity. Potentially useful in the treatment of MAO-mediated disorders such as Parkinson's disease and Alzheimer's disease. Other compounds from this series of benzisoxazoles include the following:



Compound	R1	Formula
260431	Cl	C ₉ H ₉ ClN ₂ O ₂ .HCl
260432	H	C ₉ H ₁₀ N ₂ O ₂ .HCl
260433	F	C ₉ H ₉ FN ₂ O ₂ .HCl
260434	Me	C ₁₀ H ₁₂ N ₂ O ₂ .HCl
260435	NO2	C ₉ H ₉ N ₃ O ₄ .HCl

SOURCE – Sankyo.

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PNU-95666E

230000

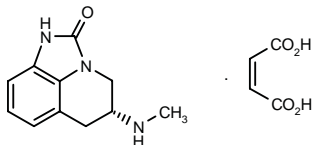
5(R)-(Methylamino)-2,4,5,6-tetrahydro-1H-imidazo[4,5,1-ij]-quinolin-2-one maleate

PNU-95666A

U-95666A

U-95666E

U-95666 (as free base)



C11-H13-N3-O.C4-H4-O4; Mol wt: 319.32

Off-white solid, m.p. 216 °C (decomp.), $[\alpha]_D^{25} -26.3^\circ$ (c 0.836, H₂O), $[\alpha]_D -27.3^\circ$ (c 1.0, H₂O); free base, m.p. 156-8 °C, $[\alpha]_D -20.9^\circ$ (c 1.0, MeOH); hydrochloride, m.p. > 310 °C, $[\alpha]_D -30.3^\circ$ (c 1.0, MeOH).

ACTION – Potent and selective dopamine D₂ receptor agonist (K_i = 9.0 nM for displacement of [³H]-U-86170 binding in cells expressing cloned mammalian D₂ receptors) with much lower affinity for dopamine D₃ receptors (K_i = 2333 nM for displacement of [³H]-(+)-7-OH-DPAT binding in cells expressing cloned mammalian receptors), moderate affinity for 5-HT_{1A} receptors (K_i = 73 nM for displacement of [³H]-(+)-8-OH-DPAT binding in cells expressing cloned mammalian receptors), and low affinity for other receptors. In rats, the compound was able to increase DOPAC levels in the median eminence (1-10 mg/kg s.c.) and decrease plasma prolactin levels (10 mg/kg s.c.), indicating agonist activity at the D₂ receptor. PNU-95666E dose-dependently increased striatal acetylcholine contents both in normal and reserpinized rats (ED₅₀ = 31.23 and 2.63 μmol/kg i.p., respectively, with intrinsic activities of 97 and 64%, respectively, compared to pramipexole [100%]), similar to other dopamine receptor agonists; no tolerance developed after chronic drug treatment and its effect was antagonized by raclopride, a D₂-like receptor antagonist. Some anxiolytic-like activity has also been suggested since the compound was able to reduce cerebellar cGMP in mice and dose-dependently attenuate (3-30 μmol/kg p.o) stress-induced elevations of this nucleotide. Potentially useful for the treatment of Parkinson's disease.

SOURCE – Pharmacia & Upjohn.

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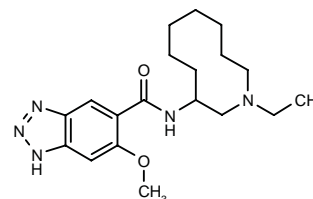
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TREATMENT OF NAUSEA AND VOMITING

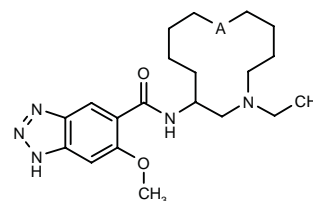
256448

N-(1-Ethylazacyclodecan-3-yl)-6-methoxybenzotriazole-5-carboxamide



C19-H29-N5-O2; Mol wt: 359.47

ACTION – Antiemetic agent and gastrointestinal motility stimulant, a representative compound from a series of 6-methoxybenzotriazole-5-carboxamides, wherein the following are also included:



Compound	A	Formula
260369	-CH2-	C ₂₁ H ₃₃ N ₅ O ₂
260370	-(CH2)2-	C ₂₂ H ₃₅ N ₅ O ₂

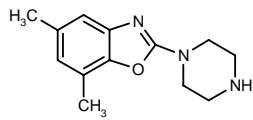
SOURCE – Dainippon.

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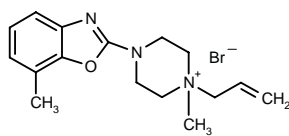
258590

5,7-Dimethyl-2-(1-piperazinyl)benzoxazole



C13-H17-N3-O; Mol wt: 231.30

ACTION – Agent for the treatment of chemotherapy- or radiation-induced emesis, gastrointestinal tract motility disorders, irritable bowel syndrome and diarrhea, a 5-HT₃ partial agonist reported to be devoid of the side effects, particularly constipation, associated with currently used pure 5-HT₃ antagonists. No mortality was observed following p.o. administration of 300 mg/kg in mice. Another compound from this series of benzoxazole derivatives is:



259356: C16-H22-Br-N3-O

SOURCE – Meiji Seika.

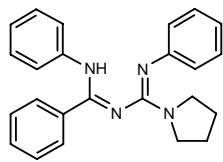
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COGNITION-ENHANCING DRUGS

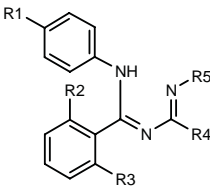
258584

N¹-Phenyl-N²-[1-(phenylimino)-1-(1-pyrrolidinyl)methyl]-benzamide

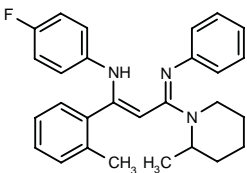


C24-H24-N4; Mol wt: 368.48

ACTION – Agent for the treatment of Alzheimer’s disease, senile dementia, multiinfarct dementia, age-related cognitive decline, attention deficit disorder, psychotic disorders, pain, sleep disorders, depression, tardive dyskinesia, Pick’s disease, Huntington’s chorea, Friederich’s ataxia, Gilles de la Tourette’s disease and Down’s syndrome, a muscarinic receptor agonist. In functional assays using human cloned receptors expressed in CHO cells, compound exhibited an EC₅₀ value of about 1 pM to about 10 pM or less at M₁, M₃ and M₅ receptors, as measured by stimulation of phosphatidylinositol hydrolysis, and an EC₅₀ value of about 1 nM to about 10 μM or less at M₂ and M₄ receptors, as measured by inhibition of forskolin-stimulated cAMP accumulation. Other related compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
259439	F	H	H	1-pyrrolidinyl	Ph	C ₂₄ H ₂₃ FN ₄
259440	H	H	H	2-Me-1-Pip	Ph	C ₂₆ H ₂₆ N ₄
259441	H	H	H	perhydro- -1,2-oxazin-2-yl	Ph	C ₂₄ H ₂₄ N ₄ O
259442	OMe	Me	Me	2-Me-1-Pip	Ph	C ₂₉ H ₃₄ N ₄ O
259444	F	Me	Me	2-Me-1-Pip	cyclohexyl	C ₂₈ H ₃₇ FN ₄
259445	F	Me	H	4-oxo-1-Pip	Ph	C ₂₈ H ₂₆ FN ₄ O
259446	F	Me	Me	4-OH-1-Pip	Ph	C ₂₇ H ₂₉ FN ₄ O
259447	OH	Me	Me	2-Me-1-Pip	Ph	C ₂₈ H ₃₂ N ₄ O
259448	F	Me	H	1-Me-cyclohexyl	Ph	C ₂₈ H ₃₀ FN ₃



259443: C28-H30-F-N3

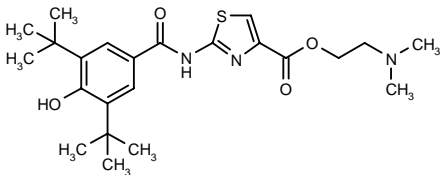
SOURCE – Pfizer.

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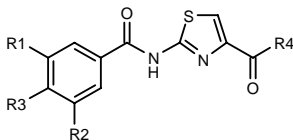
259392

2-(3,5-Di-*tert*-butyl-4-hydroxybenzamido)thiazole-4-carboxylic acid 2-(dimethylamino)ethyl ester



C23-H33-N3-O4-S; Mol wt: 447.59

ACTION – Agent for the treatment of cognitive disorders that selectively binds to muscarinic M₁ receptors in rat cortex (IC₅₀ = 0.054 μM using [³H]-pirenzepine as the ligand) and is capable of reversing scopolamine-induced hyperactivity in a swimming test in rats, with a minimum effective dose of 3 mg/kg i.p.; at the same dose, the compound was also effective in reversing scopolamine-induced disruption of performance in an 8-arm radial maze. Within this series of 2-arylamidothiazole derivatives, the following are also included:



Compound	R1=R2	R3	R4	Formula
259543	t-Bu	OH	NHCH2CH2N(Me)2	C ₂₃ H ₃₄ N ₄ O ₃ S
259544	t-Bu	OH	3-azabicyclo[3.2.2]-non-3-yl-(CH2)4NH	C ₂₉ H ₄₁ N ₃ O ₄ S
259545	t-Bu	OH	3-azabicyclo[3.2.2]-non-3-yl-(CH2)4NH	C ₃₁ H ₄₆ N ₄ O ₃ S
259546	t-Bu	OH	3-quinuclidinyl-NH	C ₂₆ H ₃₆ N ₄ O ₃ S
259547	H	OCH2Ph	3-quinuclidinyl-NH	C ₂₅ H ₂₆ N ₄ O ₃ S
259548	H	F	4-(2-MeO-Ph)-1-Piz-(CH2)3O	C ₂₅ H ₂₇ FN ₄ O ₄ S
259549	t-Bu	OH	4-(2-MeO-Ph)-1-Piz-(CH2)3O	C ₃₃ H ₄₄ N ₄ O ₅ S

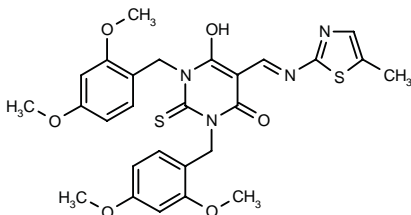
SOURCE – American Home Products.

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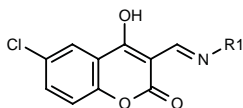
259905

1,3-Bis(2,4-dimethoxybenzyl)-6-hydroxy-5-(5-methyl-thiazol-2-yliminomethyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-4-one

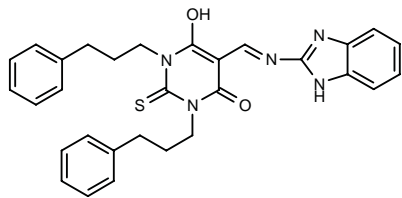


C27-H28-N4-O6-S2; Mol wt: 568.66

ACTION – Cognition-enhancing agent that binds with high affinity to the corticotropin-releasing factor (CRF)-binding protein (BP), thus causing the release of CRF from the CRF/CRF-BP complex and/or inhibiting the binding of free CRF to CRF-BP, which results in increased levels of free CRF or a CRF-related peptide such as urocortin in the brain. Compound is reported to exhibit little affinity for the CRF receptor. Also claimed for use in the treatment of chronic fatigue syndrome, atypical depression, obesity and postpartum depression. Other compounds from this series of oxocoumarin and barbituric acid derivatives include the following:



Compound	R1	Formula
260447	4-PhO-PhNHCS	C ₂₃ H ₁₅ ClN ₂ O ₄ S
260448	2-benzothiazolyl	C ₁₇ H ₉ ClN ₂ O ₃ S



260449: C30-H29-N5-O2-S

SOURCE – Neurocrine Biosciences.

REFERENCES

1. Whitten, J.P. et al. (Neurocrine Biosciences, Inc.) *Oxocoumarin and barbituric acid derivatives, their preparation and their use as ligand inhibitors of a corticotropin-releasing factor (CRF) and/or a CRF-binding protein complex*. WO 9745421.

NEUROTACTIN

257813

ACTION – Peptide from a new class of chemokines that is highly expressed in mammalian brain, reported to be involved in inflammatory processes, particularly of the brain. Antagonists of this chemokine may be useful for the treatment of brain inflammation associated with disorders such as viral encephalitis, multiple sclerosis, viral or bacterial meningitis, severe head trauma, stroke, Alzheimer’s disease and brain tumors. In addition, the peptide may be useful as a chemoprotective agent to protect progenitor cells from the cytotoxic effects of chemotherapeutic agents or radiation, as well as for inhibiting hyperproliferative myeloid-based diseases. Also useful for diagnostic purposes.

SOURCE – Millennium

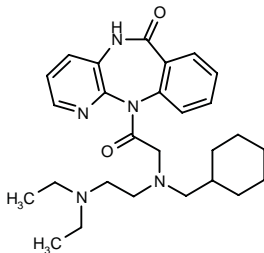
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PDC-008.004

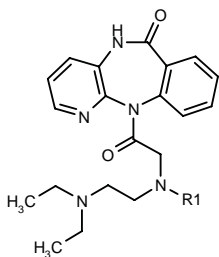
259391

11-[2-[N-(Cyclohexylmethyl)-N-[2-(diethylamino)ethyl]-amino]acetyl]-6,11-dihydro-5H-pyrido[2,3-b][1,4]benzodiazepin-6-one

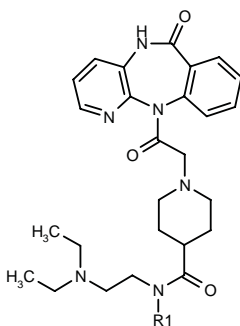


C27-H37-N5-O2; Mol wt: 463.62

ACTION – Agent for the treatment of Alzheimer’s disease and other neurological disorders with affinity for muscarinic M₂ receptors (K_i = 422 nM against [³H]-AF-DX-384 binding in rat brain preparations). *In vivo* activity and rapid brain penetration were demonstrated upon i.p. administration using the water maze test in mice. Other specifically claimed compounds include the following:



Compound	R1	Formula
259532	H	C ₂₀ H ₂₅ N ₅ O ₂
259533	(F)5-PhCH ₂	C ₂₇ H ₂₆ F ₅ N ₅ O ₂
259534	C15H31	C ₃₅ H ₅₆ N ₅ O ₂
259535	4-MeO-PhCH ₂	C ₂₈ H ₃₃ N ₅ O ₃
259536	4-NO ₂ -PhCH ₂	C ₂₇ H ₃₀ N ₅ O ₄



Compound	R1	Formula
259537	H	C ₂₆ H ₃₄ N ₆ O ₃
259538	cyclohexyl-CH ₂	C ₃₃ H ₄₆ N ₆ O ₃
259539	(F)5-PhCH ₂	C ₃₃ H ₃₅ F ₅ N ₆ O ₃

SOURCE – Pharmaceutical Discovery.

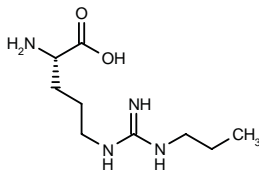
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TREATMENT OF CEREBROVASCULAR DISEASES

257923

N^ω-Propyl-L-arginine



C9-H20-N4-O2; Mol wt: 216.28

ACTION – Potent, selective and competitive neuronal nitric oxide synthase (nNOS) inhibitor (K_i = 57 nM; nNOS/iNOS = 3158 and nNOS/eNOS = 149). Potentially useful for the treatment of stroke, Alzheimer’s disease and other neurodegenerative disorders.

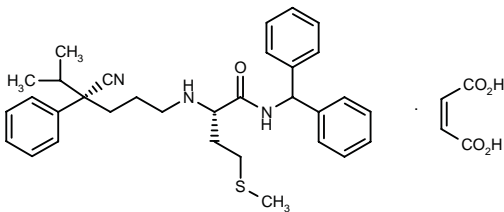
SOURCES – Univ. Michigan, Ann Arbor, MI (US); Northwestern Univ., Evanston, IL (US); Univ. Texas, San Antonio, TX (US).

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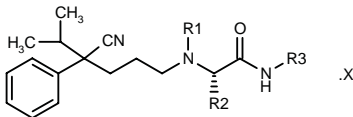
258583

N-[4(S)-Cyano-5-methyl-4-phenylhexyl]-L-methionine diphenylmethanamide maleate

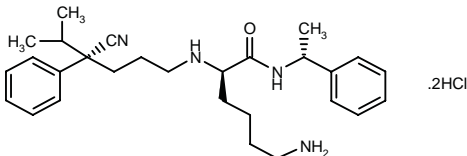


C32-H39-N3-O-S.C4-H4-O4; Mol wt: 629.81

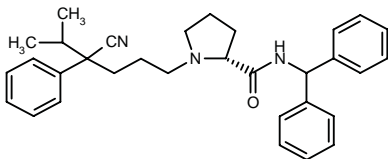
ACTION – Voltage-dependent calcium channel blocker (IC₅₀ < 3 μM in rat synaptosome preparations or cloned human cell lines expressing specific voltage-dependent calcium channels) with potential in the treatment of anoxia, ischemia, stroke, heart failure, migraine, pain, epilepsy, traumatic head or spinal injury, AIDS-related dementia or blindness, amnesia, neurodegenerative diseases, age-related memory disorders, Down’s syndrome, mood disorders, drug or alcohol withdrawal, nausea from chemotherapy and carbon monoxide or cyanide poisoning. Other related compounds include the following:



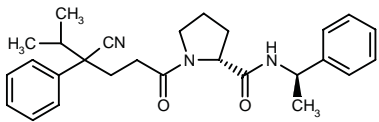
Compound	R1	R2	R3	X	Isomer	Formula
259411	H	4-OH-PhCH ₂	CH(Ph) ₂	maleate	S	C ₃₆ H ₃₉ N ₃ O ₂ ·C ₄ H ₄ O ₄
259413	H	(CH ₂) ₄ NH ₂	CH ₂ CH(Ph) ₂	2HCl		C ₃₄ H ₄₄ N ₄ O·2HCl
259414	H	CH ₂ CO ₂ Me	(R)-CH(Me)Ph	maleate	S	C ₂₇ H ₃₅ N ₃ O ₃ ·C ₄ H ₄ O ₄
259415	H	i-Pr	(S)-CH(Ph)-CONH ₂		S	C ₂₇ H ₃₆ N ₄ O ₂
259416	H	i-Pr	(S)-CH(CH ₂ OH)-CH ₂ Ph	maleate	S	C ₂₈ H ₃₉ N ₃ O ₂ ·C ₄ H ₄ O ₄
259417	Me	H	CH ₂ CH(Ph) ₂	maleate		C ₃₁ H ₃₇ N ₃ O·C ₄ H ₄ O ₄



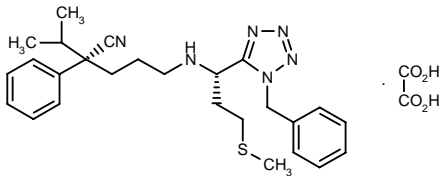
259412: C28-H40-N4-O.2HCl



259418: C32-H37-N3-O



259419: C27-H33-N3-O2



259420: C26-H34-N6-S.C2-H2-O4

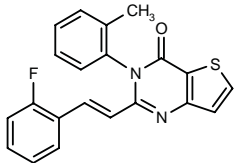
SOURCE – Lilly.

REFERENCES

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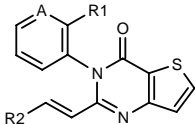
258595

2-[2-(2-Fluorophenyl)vinyl]-3-(2-methylphenyl)thieno-[3,2-*d*]pyrimidin-4(3*H*)-one



C21-H15-F-N2-O-S; Mol wt: 362.42

ACTION – Neuroprotective agent, a potent AMPA receptor antagonist. Other compounds from this series of specifically claimed (5,6)-heteroaryl-fused-pyrimidin-4-ones include the following:



Compound	R1	R2	A	Formula
259357	Cl	2-F-Ph	CH	C ₂₀ H ₁₂ ClFN ₂ OS
259358	Me	2-Pyr	CH	C ₂₀ H ₁₅ N ₃ OS
259359	Me	2-Cl-Ph	CH	C ₂₁ H ₁₅ ClN ₂ OS
259360	CF3	2-F-Ph	CH	C ₂₁ H ₁₂ F ₄ N ₂ OS
259361	Cl	2-Me-4-thiazolyl	N	C ₁₇ H ₁₁ ClN ₄ OS ₂
259362	Me	2-Me-4-thiazolyl	N	C ₁₈ H ₁₄ N ₄ OS ₂
259363	Cl	2-Pyr	CH	C ₁₉ H ₁₂ ClN ₃ OS
259364	Cl	2-OH-Ph	CH	C ₂₀ H ₁₃ ClN ₂ O ₂ S

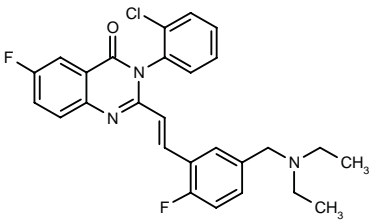
SOURCE – Pfizer.

REFERENCES

1. Chenard, B.L. et al. (Pfizer, Inc.) *Novel 2,3-disubstd.-(5,6)-heteroaryl/fused-pyrimidin-4-ones*. EP 807633.

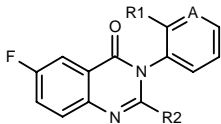
258990

3-(2-Chlorophenyl)-2-[2-[5-(diethylaminomethyl)-2-fluorophenyl]vinyl]-6-fluoroquinazolin-4(3*H*)-one



C27-H24-Cl-F2-N3-O; Mol wt: 479.96

ACTION – Neuroprotective agent, a potent AMPA receptor antagonist with an IC₅₀ value < 5 μM against AMPA receptor activation-induced ⁴⁵Ca²⁺ uptake in rat cerebellar granule cell membranes. Other compounds from this series of specifically claimed 2,3-disubstituted-4(3*H*)-quinazolinones include the following:



Compound	R1	R2	A	Formula
259496	Cl	6-[CH2N(Et)2]-2-Pyr-CH=CH	CH	C ₂₆ H ₂₄ ClFN ₄ O
259497	Cl	4-[CH2N(Et)2]-2-Pyr-CH=CH	CH	C ₂₆ H ₂₄ ClFN ₄ O
259498	Cl	6-(EtNHCH2)-2-Pyr-CH=CH	CH	C ₂₄ H ₂₀ ClFN ₄ O
259499	Br	6-[CH2N(Et)2]-2-Pyr-CH=CH	CH	C ₂₆ H ₂₄ BrFN ₄ O
259500	Cl	6-(MeOCH2)-2-Pyr-CH=CH	CH	C ₂₃ H ₁₇ ClFN ₃ O ₂
259501	Me	2-Me-4-thiazolyl-CH=CH	N	C ₂₀ H ₁₅ FN ₄ OS
259502	Cl	4-Me-2-pyrimidinyl-CH=CH	CH	C ₂₁ H ₁₄ ClFN ₄ O
259503	Cl	6-(i-PrNHCH2)-2-Pyr-CH2CH2	CH	C ₂₅ H ₂₄ ClFN ₄ O
259504	Me	2-F-5-[CH2N(Et)2]-PhCH=CH	N	C ₂₇ H ₂₆ F ₂ N ₄ O

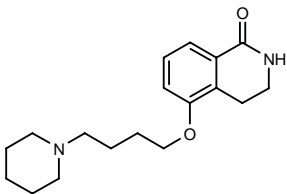
SOURCE – Pfizer.

REFERENCES

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259066

5-[4-(1-Piperidiny)butoxy]-3,4-dihydroisoquinolin-1(2*H*)-one



C18-H26-N2-O2; Mol wt: 302.42

ACTION – Neuroprotective agent, a potent inhibitor of NAD^+ ADP-ribosyltransferase, also known as poly(ADP) polymerase, poly(adenosine diphosphate ribose) polymerase (PARP) and poly(adenosine 5'-diphosphoribose) synthetase (PARS). The compound significantly reduced infarct volume in a focal cerebral ischemia model in rats induced by middle cerebral artery and carotid artery occlusion at the dose range of 5-20 mg/kg i.p.

SOURCES – Guilford; Univ. Pennsylvania School Med., Philadelphia, PA (US).

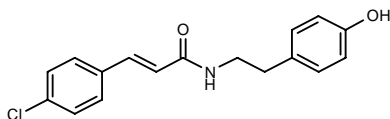
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259751

3-(4-Chlorophenyl)-*N*-[2-(4-hydroxyphenyl)ethyl]-2(*E*)-propenamide

4-Chloro-*N*-[2-(4-hydroxyphenyl)ethyl]cinnamamide



C17-H16-Cl-N-O2; Mol wt: 301.77

ACTION – Potent and selective antagonist of NMDA NR1A/2B receptors, a substituted cinnamide compound that acts as a functional antagonist at the NMDA NR1A/2B subtype ($\text{IC}_{50} = 0.17 \pm 0.02 \mu\text{M}$) compared to NR1A/2A or NR1A/2C subtypes ($\text{IC}_{50} > 300 \mu\text{M}$).

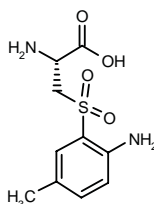
SOURCES – Acea; CoCensys; Univ. Oregon, Eugene, OR (US); Warner-Lambert.

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259757

S-(2-Amino-5-methylphenyl)-L-cysteine *S,S*-dioxide



C10-H14-N2-O4-S; Mol wt: 258.29

ACTION – Potent inhibitor of mammalian kynureninase ($\text{IC}_{50} = 11 \mu\text{M}$) that inhibits the interferon gamma-induced synthesis of quinolinic acid in human macrophages. Title compound may have utility in pathogenic states involving abnormal quinolinic acid levels such as in spinal cord injury.

SOURCE – Glaxo Wellcome.

REFERENCES

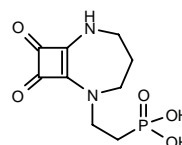
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EAA-090*

189797

2-[8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]-ethylphosphonic acid

WAY-126090



C9-H13-N2-O5-P; Mol wt: 260.19

Hydrate, yellow solid, m.p. 260-78 °C.

ACTION – Potent and selective NMDA receptor antagonist, as shown both *in vitro* by its high affinity for the NMDA receptor ($\text{IC}_{50} = 30 \text{ nM}$ for displacement of $[^3\text{H}]$ -CPP binding in rat brain membranes) and antagonist activity ($\text{IC}_{50} = 7.6 \mu\text{M}$) in the stimulated $[^3\text{H}]$ -TCP binding assay, and *in vivo* by blockade of NMDA-induced lethality in mice ($\text{ED}_{50} = 2.1 \text{ mg/kg i.p.}$). Compound exhibited marked neuroprotective properties in the rat focal ischemia model of severe stroke involving occlusion of the middle cerebral artery (57% decrease in infarct volume at 10 mg/kg i.v.). Based on its preclinical profile, the compound may offer advantages over existing NMDA antagonists for the treatment of neurological disorders such as stroke and head trauma, and it is currently under clinical evaluation as a neuroprotective agent for stroke.

SOURCE – Wyeth-Ayerst.

REFERENCES

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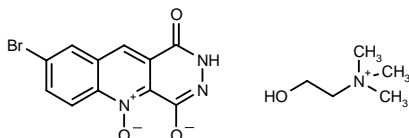
*Identified compound **189797** (see **187354**) Drug Data Rep 1992, 14(11): 964.

MRZ-2/570

251548

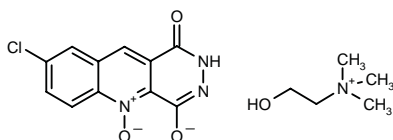
8-Bromopyridazino[4,5-*b*]quinoline-1,4(2*H*,3*H*)-dione *N*⁵-oxide choline salt

MRZ-2/502 (free acid)



C16-H19-Br-N4-O4; Mol wt: 411.25

ACTION – Systemically active NMDA receptor antagonist acting at the strychnine-insensitive glycine recognition site (glycine_B antagonist) that shows moderate affinity for this site ($IC_{50} = 104.0 \pm 16.1$ nM for displacement of [³H]-MDL-105519 binding in rat cortical membranes). It exhibited antagonist properties both *in vitro* (inhibition of steady-state NMDA/glycine-induced currents in cultured rat hippocampal neurons: $IC_{50} = 0.14 \pm 0.02$ μ M) and *in vivo*, as demonstrated by inhibition of NMDA-induced responses in rat spinal cord neurons ($ID_{50} = 4.5 \pm 0.7$ mg/kg i.v.; $ID_{50} > 16$ mg/kg i.v. for AMPA-induced responses) and by inhibition of pentylenetetrazol-, NMDA- and maximal electroshock (MES)-induced convulsions in mice ($ED_{50} = 10.6, 58.3$ and 12.8 mg/kg i.p., respectively). MRZ-2/570 also exhibited neuroprotective properties in several behavioral test in rodents (NMDA-induced choline acetyltransferase loss and global ischemia-induced cell loss) and attenuated PCP- and amphetamine-induced hyperlocomotion and haloperidol-induced catalepsy. Compound also inhibited acquisition and expression of morphine-induced conditioned place preference in rats and attenuated naloxone-precipitated withdrawal syndrome in morphine-dependent mice. Potentially useful in the treatment of disorders involving disturbances of glutamatergic transmission such as acute excitotoxicity, chronic neurodegenerative diseases, disorders related to long-term plastic changes in the CNS (chronic pain, drug tolerance, dependence and addiction), epilepsy, tardive dyskinesia, schizophrenia, anxiety, depression, visceral pain, spasticity and tinnitus. Another tricyclic pyrido-phthalazine-dione derivative:



MRZ-2/576 [251549]: C16-H19-Cl-N4-O4

MRZ-2/514 (free acid)

SOURCE – Merz.

REFERENCES

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10. Parsons, C.G. et al. Novel antagonists of the glycine site of the NMDA receptor - Electrophysiological and biochemical characterisation. Soc Neurosci Abstr 1996, 22(Part 2): Abstr 604.17.

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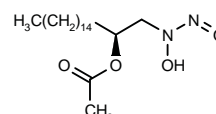
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POECILLANOSINE

259163

Acetic acid 1(*S*)-(1-hydroxy-2-oxohydrazinomethyl)hexadecyl ester



C19-H38-N2-O4; Mol wt: 358.52

$[\alpha]_D^{25} -20.2^\circ$ (*c* 0.1, MeOH).

ACTION – Free radical scavenger, a nitrosohydroxy-alkylamine isolated from the marine sponge *Poecillastra spec. aff. tenuilaminaris* that inhibits lipid peroxidation in rat brain homogenates ($IC_{50} = 0.04$ μ M). It also exhibits cytotoxic activity against murine P388 leukemia cells ($IC_{50} = 1.8$ μ g/ml).

SOURCE – Kirin Brewery.

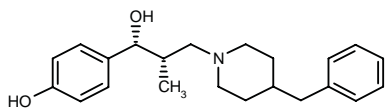
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RO-25-6981

259847

(1*R*,2*S*)-3-(4-Benzylpiperidin-1-yl)-1-(4-hydroxyphenyl)-2-methyl-1-propanol



C22-H29-N-O2; Mol wt: 339.48

ACTION – Neuroprotective agent, a potent and selective, activity-dependent blocker of NMDA receptors containing the NR2B subunit. Ro-25-6191 displaced [³H]-MK-801 binding in rat forebrain membranes (IC₅₀ = 0.003 and 149 μM, respectively, for high- and low-affinity sites) and inhibited the activity of NMDA receptors expressed in *Xenopus* oocytes (IC₅₀ = 0.009, 0.017 and 52 μM for NMDA receptors containing NR1C/2B, NR1F/2B or NR1C/2A subunits, respectively), and it also inhibited the NMDA NR2B receptor activity in cultured rat cortical neurons (IC₅₀ = 0.015 μM). Compound protected cultured cortical neurons against both glutamate toxicity (IC₅₀ = 0.4 μM) and oxygen+glucose deprivation (IC₅₀ = 0.04 μM), whereas it showed no protective effects against kainate toxicity and only weak Na⁺ and Ca²⁺ channel-blocking activity. *In vivo* in a model of permanent focal brain ischemia in rats, it reduced cortical infarct volume by 37 ± 5% at a dose of 1.9 mg/kg by i.v. bolus 5 min following occlusion, followed by 4.4 mg/kg/h for 6 h, with no cardiovascular side effects or motor impairment; compound also protected against sound-induced seizures in DBA/2J mice (ED₅₀ = 12 mg/kg i.p.). The compound is also reported to have potential in the treatment of Parkinson's disease.

SOURCE – Roche.

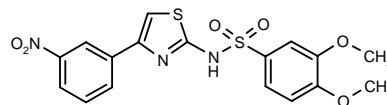
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RO-61-8048

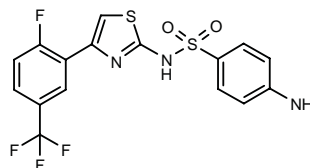
259179

3,4-Dimethoxy-N-[4-(3-nitrophenyl)-2-thiazolyl]benzenesulfonamide



C17-H15-N3-O6-S2; Mol wt: 421.44

ACTION – Potent, high-affinity and orally active inhibitor of kynurenine 3-hydroxylase (kynurenine 3-monooxygenase), as shown *in vitro* (IC₅₀ = 37 ± 3 nM using mitochondrial rat kidney enzyme and L-[3-³H]-kynurenine as substrate) and *ex vivo* after oral administration to rats (ED₅₀ = 1.2 and 4.7 μmol/kg p.o., respectively, in kidney and liver) and gerbils (ED₅₀ = 5.5, 0.8 and 0.4 μmol/kg p.o., respectively, in brain, kidney and liver). An increase in extracellular kynurenic acid levels in rat hippocampus was observed at doses of 50 and 100 μmol/kg p.o. of the compound, thus suggesting the ability of Ro-61-8048 to inhibit kynurenine 3-hydroxylase *in vivo*. Another N-(4-phenylthiazol-2-yl)benzenesulfonamide with similar characteristics is:



258530: C16-H11-F4-N3-O2-S2

Kynurenine 3-hydroxylase is a target for neuroprotective drug discovery based on the rationale that inhibitors of the enzyme would result in a decrease in quinolinic acid, increased levels of which appear to be associated with brain inflammation, and an increase in the production of kynurenic acid, a glutamate antagonist with neuroprotective properties.

SOURCE – Roche.

REFERENCES

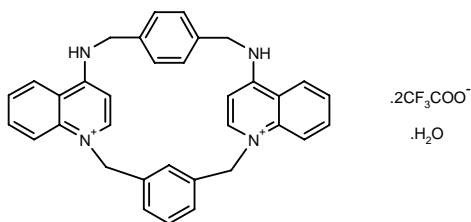
- Röver, S. et al. *Synthesis and biochemical evaluation of N-(4-phenylthiazol-2-yl)benzenesulfonamides as high-affinity inhibitors of kynurenine 3-hydroxylase*. J Med Chem 1997, 40(26): 4378.
- Röver, S. et al. *High-affinity inhibitors of rat kynurenine 3-hydroxylase*. 1st Ital Swiss Meet Med Chem (Sept 23-26, Torino) 1997, 50.

MISCELLANEOUS NEUROLOGIC DRUGS

UCL-1684

259287

1,9-Diazonia-17,24-diazaheptacyclo[23.6.2.2^{9,16}.21^{9,22}.13⁷.0^{10,14}.0^{26,31}]octatriaconta-1(31),3,5,7(38),9,11,13,15,19,21,25,27,29,34,36-hexadecaene bis(trifluoroacetate) hydrate



C38-H30-F6-N4-O4.H2-O; Mol wt: 738.69

ACTION – Agent for the treatment of myotonic muscular dystrophy, gastrointestinal motility disorders, memory disorders, narcolepsy and alcohol abuse, a potent, nonpeptide blocker of small-conductance Ca^{2+} -activated potassium (SK_{Ca}) channels. *In vitro*, it exhibited an IC_{50} value of 3 ± 1 nM for inhibition of afterhyperpolarization in cultured rat sympathetic neurons, being > 100-fold more potent than dequalinium and similar to apamin.

SOURCE – Aristotelian Univ. Thessaloniki, Thessaloniki (GR); Univ. Granada, Granada (ES); Univ. Coll. London, London (GB).

REFERENCES

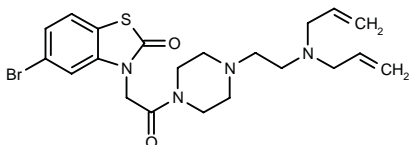
1. Campos Rosa, J. et al. *Bis-quinolinium cyclophanes: 6,10-Diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane (UCL 1684), the first nanomolar, non-peptidic blocker of the apamin-sensitive Ca^{2+} -activated K^+ channel.* J Med Chem 1998, 41(1): 2.

RESPIRATORY DRUGS

ASTHMA THERAPY

258996

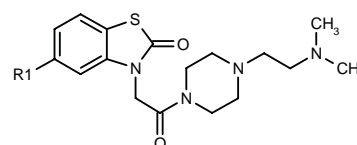
5-Bromo-3-[2-[4-[2-(diallylamino)ethyl]piperazin-1-yl]-2-oxoethyl]benzothiazol-2(3H)-one



C21-H27-Br-N4-O2-S; Mol wt: 479.43

ACTION – Antiasthmatic agent with a direct bronchospasmolytic action on isolated guinea pig tracheal ring preparations, as evidenced by inhibition of spontaneous tone

($\text{EC}_{50} = 1.7 \mu\text{M}$) and contractions elicited by barium chloride ($\text{EC}_{50} = 4.9 \mu\text{M}$). *In vivo* efficacy was demonstrated by inhibition of PAF-induced bronchoconstriction (77% at 3 mg/kg i.v.) in guinea pigs. Compound also inhibited bronchial hyperreactivity elicited by PAF, substance P or bradykinin, with about 80, 73 and 55% inhibition, respectively, at a dose of 6 mg/kg i.v. in guinea pigs. Marked activity was also demonstrated in a series of conventional *in vivo* models including those designed to evaluate inhibition of protein extravasation or bronchospasm induced by mediator release from immunocompetent cells or by the release of neuropeptides from C-fibers. A representative compound within a series of specifically claimed benzothiazolinones, wherein the following are also included:



Compound	R1	Formula
260356	Br	$\text{C}_{17}\text{H}_{23}\text{BrN}_4\text{O}_2\text{S}$
260357	Cl	$\text{C}_{17}\text{H}_{23}\text{ClN}_4\text{O}_2\text{S}$

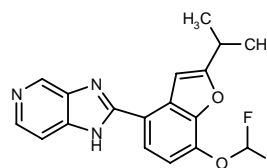
SOURCE – Klinge Pharma.

REFERENCES

1. Eisenburger, R. et al. (Klinge Pharma GmbH) *Benzothiazolinones as anti-asthmatic agents.* WO 9743282.

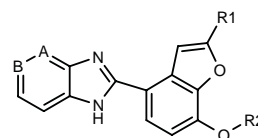
259000

2-[7-(Difluoromethoxy)-2-isopropylbenzofuran-4-yl]-1H-imidazo[4,5-c]pyridine



C18-H15-F2-N3-O2; Mol wt: 343.33

ACTION – A selective inhibitor of phosphodiesterase type IV (PDE IV; $-\log\text{IC}_{50} = 8.38$) reported to possess low toxicity and high bioavailability. Potentially useful for the treatment of asthma, dermatoses, erectile dysfunction and a wide range of acute and chronic inflammatory disorders. A representative compound from a series of imidazopyridines, wherein the following are also included:



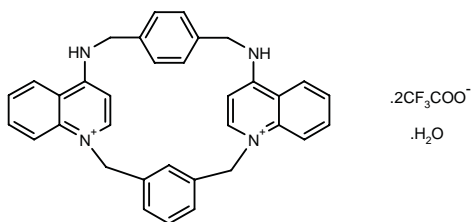
Compound	R1	R2	A	B	Formula
260043	i-Pr	Me	N	CH	$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$
260044	i-Pr	CHF2	N	CH	$\text{C}_{18}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_2$
260046	cyclopentyl	Me	CH	N	$\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2$
260048	i-Pr	Me	CH	N	$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$

MISCELLANEOUS NEUROLOGIC DRUGS

UCL-1684

259287

1,9-Diazonia-17,24-diazaheptacyclo[23.6.2.2^{9,16}.21^{9,22}.13⁷.0^{10,14}.0^{26,31}]octatriaconta-1(31),3,5,7(38),9,11,13,15,19,21,25,27,29,34,36-hexadecaene bis(trifluoroacetate) hydrate



C38-H30-F6-N4-O4.H2-O; Mol wt: 738.69

ACTION – Agent for the treatment of myotonic muscular dystrophy, gastrointestinal motility disorders, memory disorders, narcolepsy and alcohol abuse, a potent, nonpeptide blocker of small-conductance Ca^{2+} -activated potassium (SK_{Ca}) channels. *In vitro*, it exhibited an IC_{50} value of 3 ± 1 nM for inhibition of afterhyperpolarization in cultured rat sympathetic neurons, being > 100-fold more potent than dequalinium and similar to apamin.

SOURCE – Aristotelian Univ. Thessaloniki, Thessaloniki (GR); Univ. Granada, Granada (ES); Univ. Coll. London, London (GB).

REFERENCES

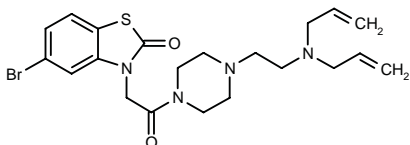
1. Campos Rosa, J. et al. *Bis-quinolinium cyclophanes: 6,10-Diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecapane (UCL 1684), the first nanomolar, non-peptidic blocker of the apamin-sensitive Ca^{2+} -activated K^+ channel.* J Med Chem 1998, 41(1): 2.

RESPIRATORY DRUGS

ASTHMA THERAPY

258996

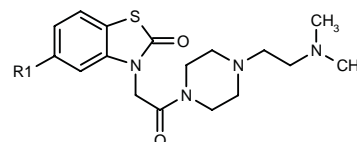
5-Bromo-3-[2-[4-[2-(diallylamino)ethyl]piperazin-1-yl]-2-oxoethyl]benzothiazol-2(3H)-one



C21-H27-Br-N4-O2-S; Mol wt: 479.43

ACTION – Antiasthmatic agent with a direct bronchospasmolytic action on isolated guinea pig tracheal ring preparations, as evidenced by inhibition of spontaneous tone

($\text{EC}_{50} = 1.7 \mu\text{M}$) and contractions elicited by barium chloride ($\text{EC}_{50} = 4.9 \mu\text{M}$). *In vivo* efficacy was demonstrated by inhibition of PAF-induced bronchoconstriction (77% at 3 mg/kg i.v.) in guinea pigs. Compound also inhibited bronchial hyperreactivity elicited by PAF, substance P or bradykinin, with about 80, 73 and 55% inhibition, respectively, at a dose of 6 mg/kg i.v. in guinea pigs. Marked activity was also demonstrated in a series of conventional *in vivo* models including those designed to evaluate inhibition of protein extravasation or bronchospasm induced by mediator release from immunocompetent cells or by the release of neuropeptides from C-fibers. A representative compound within a series of specifically claimed benzothiazolinones, wherein the following are also included:



Compound	R1	Formula
260356	Br	$\text{C}_{17}\text{H}_{23}\text{BrN}_4\text{O}_2\text{S}$
260357	Cl	$\text{C}_{17}\text{H}_{23}\text{ClN}_4\text{O}_2\text{S}$

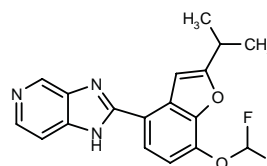
SOURCE – Klinge Pharma.

REFERENCES

1. Eisenburger, R. et al. (Klinge Pharma GmbH) *Benzothiazolinones as anti-asthmatic agents.* WO 9743282.

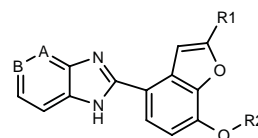
259000

2-[7-(Difluoromethoxy)-2-isopropylbenzofuran-4-yl]-1H-imidazo[4,5-c]pyridine

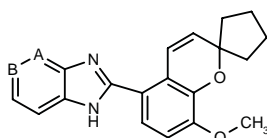


C18-H15-F2-N3-O2; Mol wt: 343.33

ACTION – A selective inhibitor of phosphodiesterase type IV (PDE IV; $-\log\text{IC}_{50} = 8.38$) reported to possess low toxicity and high bioavailability. Potentially useful for the treatment of asthma, dermatoses, erectile dysfunction and a wide range of acute and chronic inflammatory disorders. A representative compound from a series of imidazopyridines, wherein the following are also included:



Compound	R1	R2	A	B	Formula
260043	i-Pr	Me	N	CH	$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$
260044	i-Pr	CHF2	N	CH	$\text{C}_{18}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_2$
260046	cyclopentyl	Me	CH	N	$\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2$
260048	i-Pr	Me	CH	N	$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$



Compound	A	B	Formula
260045	N	CH	C ₂₀ H ₁₉ N ₃ O ₂
260047	CH	N	C ₂₀ H ₁₉ N ₃ O ₂

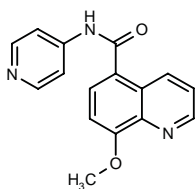
SOURCE – Byk Gulden.

REFERENCES

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259026

8-Methoxy-*N*-(4-pyridyl)quinoline-5-carboxamide



C16-H13-N3-O2; Mol wt: 279.30

ACTION – An inhibitor of phosphodiesterase type IV (PDE IV) and the production of tumor necrosis factor (TNF) with potential in the treatment of a variety of disorders including asthma, allergic and inflammatory disorders, and fungal infections.

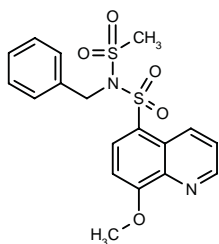
SOURCE – Chiroscience.

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1. Dyke, H.J. et al. (Chiroscience, Ltd.) *Quinoline carboxamides as TNF inhibitors and as PDE-IV inhibitors*. WO 9744036.

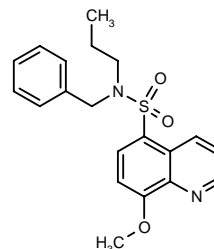
259042

N-Benzyl-*N*-(methanesulfonyl)-8-methoxyquinoline-5-sulfonamide



C18-H18-N2-O5-S2; Mol wt: 406.47

ACTION – An inhibitor of phosphodiesterase type IV (PDE IV) and the production of tumor necrosis factor (TNF) with potential in the treatment of a variety of disorders including asthma, allergic and inflammatory disorders, and fungal infections. Another specifically claimed compound from this series of quinoline sulfonamides is:



260298: C20-H22-N2-O3-S

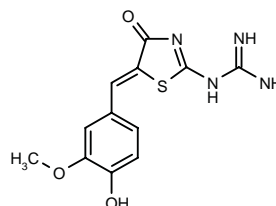
SOURCE – Chiroscience.

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1. Dyke, H.J. and Montana, J.G. (Chiroscience, Ltd.) *Quinoline sulfonamides as TNF inhibitors and as PDE-IV inhibitors*. WO 9744322.

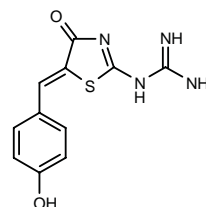
256478

N-[5-(4-Hydroxy-3-methoxybenzylidene)-4-oxo-3,4-dihydrothiazol-2-yl]guanidine



C12-H12-N4-O3-S; Mol wt: 292.31

ACTION – Antiallergic agent shown to inhibit compound 48/80-induced histamine release from rat peritoneal mast cells (78.5 and 94.6% inhibition at 0.1 and 1 μM, respectively). Antihistaminic activity was tested *in vitro* by inhibition of histamine-induced guinea pig ileum contractions (12.2% at 1 μM). *In vivo*, it inhibited the picryl chloride-induced delayed-type hypersensitivity reaction in sensitized mice, with 49.2% inhibition at 10 mg/kg p.o. Another related compound is:



260371: C11-H10-N4-O2-S

SOURCE – Hisamitsu.

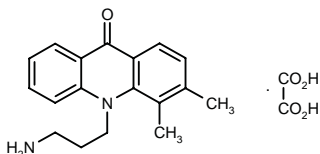
REFERENCES

1. Kubo, J. et al. (Hisamitsu Pharm. Co., Ltd.) *Novel benzylidene derivs*. JP 97255669.

ER-27319

238015

10-(3-Aminopropyl)-3,4-dimethylacridin-9(10*H*)-one oxalate



C18-H20-N2-O.C2-H2-O4; Mol wt: 370.40

ACTION – Potent and selective inhibitor of Syk activation and phosphorylation in mast cells that appears to specifically inhibit the interaction of Syk with the high-affinity IgE receptor (FcεRI) γ subunit ITAM (immunoreceptor tyrosine-based activation motif). The compound inhibited antigen-induced responses in rat peritoneal mast cells, blocking the release of histamine, peptidoleukotrienes and PGD₂ by > 80% at 30 μM, as well as the anti-human IgE antibody-stimulated release of histamine and arachidonic acid in human cultured mast cells (> 80% at 30 μM). ER-27319 may be potentially useful for the treatment of allergic diseases.

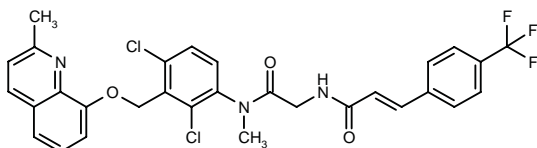
SOURCE – Eisai.

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1. Miyamoto, M. et al. (Eisai Co., Ltd.) *Acridone derivs. and their preparation*. JP 95316135.
2. Yoshiuchi, T. et al. (Eisai Co., Ltd.) *Acridone cpds*. JP 97249650, WO 9712872.
3. Moriya, K. et al. *ER-27319 inhibits the release of antigen-induced allergic mediators from mast cells by blocking the association between syk and ITAM*. FASEB J 1996, 10(6): Abst 1562.
4. Moriya, K. et al. *ER-27319, an acridone-related compound, inhibits release of antigen-induced allergic mediators from mast cells by selective inhibition of Fcε receptor I-mediated activation of Syk*. Proc Natl Acad Sci USA 1997, 94(23): 12539.

256318

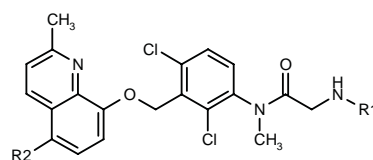
*N*¹-Methyl-*N*¹-[2,4-dichloro-3-(2-methylquinolin-8-yloxy-methyl)phenyl]-*N*^α-[4-(trifluoromethyl)cinnamoyl]-glycinamide



C30-H24-Cl2-F3-N3-O3; Mol wt: 602.44

ACTION – Bradykinin antagonist, as demonstrated *in vitro* in binding (IC₅₀ = 9.0 nM, K_i = 1.0 nM against [³H]-bradykinin binding to B₂ receptors in guinea pig ileum preparations) and functional assays (IC₅₀ = 44.0 nM for inhibition of bradykinin-induced guinea pig ileum contractions). Compound exhibited a prolonged inhibitory effect *in vitro* on bradykinin-induced rabbit jugular vein contractions at 10 μM. Potentially useful in the treatment or prevention of a wide variety of bradykinin-mediated disorders including allergic and inflammatory disorders such as asthma, bronchitis, chronic obstructive pulmonary disease, various types of shock and rheumatoid arthritis. A representative compound from a series of fluoroalkyl- and fluoralkoxy-

substituted heterocyclic compounds, wherein the following are also included:



Compound	R1	R2	Formula
259573	(E)-4-CF3-PhCH=CHCO	Me	C ₃₁ H ₂₆ Cl ₂ F ₃ N ₃ O ₃
259574	4-CF3-PhCH2CO	H	C ₂₉ H ₂₄ Cl ₂ F ₃ N ₃ O ₃
259575	4-(CF3O)-PhCH2CO	H	C ₂₉ H ₂₄ Cl ₂ F ₃ N ₃ O ₄
259576	3-CF3-PhNHCS	H	C ₂₈ H ₂₃ Cl ₂ F ₃ N ₄ O ₂ S

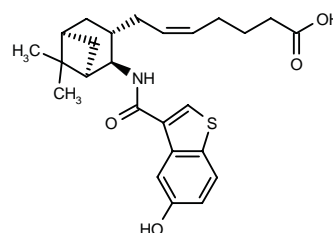
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Wagner, A. et al. (Hoechst AG) *Fluoroalkyl- and fluoralkoxy-substd. heterocyclic bradykinin antagonists*. EP 796848, JP 98007656.

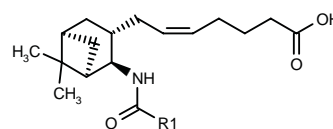
257050

(1*R*,2*R*,3*S*,5*S*)-7-[2-(5-Hydroxybenzothiophen-3-ylcarboxamido)-6,6-dimethylbicyclo[3.1.1]hept-3-yl]-5(*Z*)-heptenoic acid



C25-H31-N-O4-S; Mol wt: 441.58

ACTION – Antiallergic and antiasthmatic agent, a potent and specific prostaglandin D₂ (PGD₂) receptor antagonist (IC₅₀ = 0.4 and 1.0 nM, respectively, for inhibition of [³H]-PGD₂ binding and PGD₂-induced CAMP formation in human platelets) with much lower affinity for the thromboxane A₂ (TXA₂) receptor (IC₅₀ = 96 nM for inhibition of [³H]-(+)-S-145 binding in human platelet membranes) and no activity against PGI₂ receptors (IC₅₀ > 10 μM for inhibition of carbacyclin-induced cAMP formation in human platelets). It exhibited good anti-inflammatory and antiallergic properties in guinea pigs using a rhinitis model (ED₅₀ = 2.1 mg/kg p.o. for inhibition of antigen-induced increase in intranasal pressure) and a conjunctivitis model (ED₅₀ = 0.12 and 2.0 mg/kg topically, respectively, for inhibition of PGD₂- and antigen-induced increases in conjunctival microvascular permeability). In addition, the compound (10 mg/kg p.o.) inhibited (70%) the increase in airways resistance induced by antigen inhalation in conscious guinea pigs. Other 6,6-dimethylbicyclo[3.1.1]heptane derivatives include the following:



Compound	R1	Formula
257051	5-F-3-benzothieryl	C ₂₅ H ₃₀ FNO ₃ S
257052	3-thienyl	C ₂₁ H ₂₉ NO ₃ S

SOURCE – Shionogi.

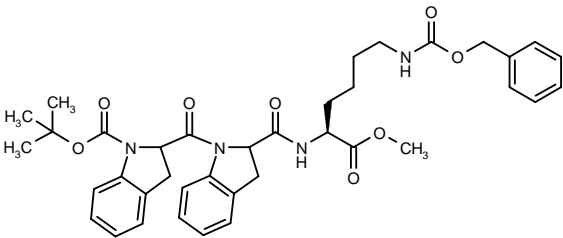
REFERENCES

1. Ohtani, M. et al. (Shionogi & Co., Ltd.) *Bicyclic amino derivs. and PGD₂ antagonist containing the same*. WO 9700853.

2. Tsuri, T. et al. *Bicyclo[2.2.1]heptane and 6,6-dimethylbicyclo[3.1.1]heptane derivatives: Orally active, potent, and selective prostaglandin D₂ receptor antagonists*. J Med Chem 1997, 40(22): 3504.

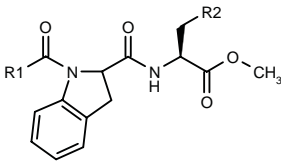
257777

N^ε-(Benzyloxycarbonyl)-N^α-[1-[1-(*tert*-butoxycarbonyl)indolin-2-ylcarbonyl]-L-lysine methyl ester

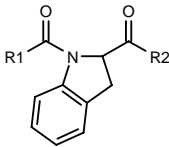


C38-H44-N4-O8; Mol wt: 684.79

ACTION – Antiasthmatic and immunosuppressive agent, an immunophilin ligand. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
259739	1-(t-BuOCO)-4-Pip	t-BuOCONH(CH2)3	C ₃₂ H ₄₈ N ₄ O ₈
259740	4-Pip	(CH2)3NH2	C ₂₂ H ₃₂ N ₄ O ₄
259741	1-(t-BuOCO)-2-indoliny	t-BuOCONH(CH2)3	C ₃₅ H ₄₆ N ₄ O ₈
259742	2-indoliny	(CH2)3NH2	C ₂₅ H ₃₀ N ₄ O ₄
259743	t-BuO	(CH2)3NHCO2CH2Ph	C ₂₉ H ₃₇ N ₃ O ₇
259744	t-BuO	Ph	C ₂₄ H ₂₈ N ₂ O ₅
259748	1-(4-MeO-Ph-CH2CO)-4-Pip	(CH2)3NHCO2CH2Ph	C ₃₉ H ₄₆ N ₄ O ₈



Compound	R1	R2	Formula
259745	t-BuO	4-Pip-NH	C ₁₉ H ₂₇ N ₃ O ₃
259746	t-BuO	4-(4-morpholinyl-COCH2)-1-Piz	C ₂₄ H ₃₄ N ₄ O ₅
259747	1-(t-BuOCO)-4-Pip	4-(4-morpholinyl-COCH2)-1-Piz	C ₃₀ H ₄₃ N ₅ O ₆

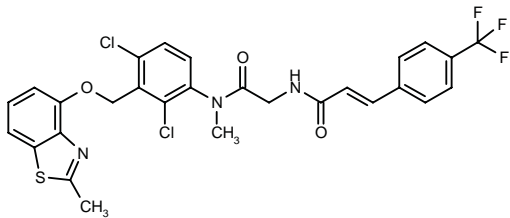
SOURCE – Asta Medica.

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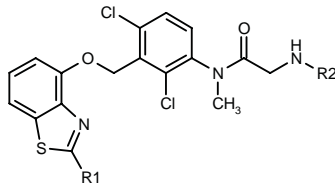
258702

N¹-[2,4-Dichloro-3-(2-methylbenzothiazol-4-yloxymethyl)phenyl]-N¹-methyl-N^α-[4-(trifluoromethyl)cinnamoyl]glycinamide



C28-H22-Cl2-F3-N3-O3-S; Mol wt: 608.46

ACTION – Bradykinin antagonist, as demonstrated *in vitro* in binding (IC₅₀ < 0.1 μM against [³H]-bradykinin binding to B₂ receptors in guinea pig ileum preparations) and functional assays (IC₅₀ < 1 μM against bradykinin-induced guinea pig pulmonary artery contractions). Potentially useful in the treatment or prevention of allergic or inflammatory disorders including asthma, bronchitis, rhinitis, septic shock, rheumatoid arthritis and psoriasis. Other compounds from this series of sulfur-containing heterocyclic bradykinin antagonists include the following:



Compound	R1	R2	Formula
259606	Me	(E)-vinyl-CH=CHCO	C ₂₃ H ₂₁ Cl ₂ N ₃ O ₃ S
259607	Me	(E)-2-furyl-CH=CHCO	C ₂₅ H ₂₁ Cl ₂ N ₃ O ₄ S
259608	Me	(E)-SO ₂ CH=CHPh	C ₂₆ H ₂₃ Cl ₂ N ₃ O ₄ S ₂
259609	Me	(E)-COCH=CHPh	C ₂₇ H ₂₃ Cl ₂ N ₃ O ₃ S
259610	Ph	(E)-3-MeO-PhCH=CHCO	C ₃₃ H ₂₇ Cl ₂ N ₃ O ₄ S

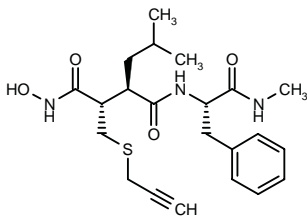
SOURCE – Hoechst Marion Roussel.

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258979

N-[4-(Hydroxyamino)-2(*R*)-isobutyl-3(*S*)-(2-propynyl)sulfanylmethyl)succinyl]-L-phenylalanine methylamide



C22-H31-N3-O4-S; Mol wt: 433.56

ACTION – Inhibitor of the formation of soluble human CD23 (sCD23, low-affinity IgE receptor FcεRII) and of the release of tumor necrosis factor (TNF), with potential for the treatment of conditions associated with the overproduction of sCD23 such as allergy, inflammation and

autoimmune diseases, as well as disease states associated with the overproduction of TNF such as rheumatoid arthritis, septic shock, Crohn's disease and cachexia. It produced 91 and 83% inhibition of sCD23 and TNF production, respectively, at 1 μ M, whereas it exhibited reduced activity against collagenase ($IC_{50} > 10 \mu$ M) compared to other related hydroxamic acid compounds.

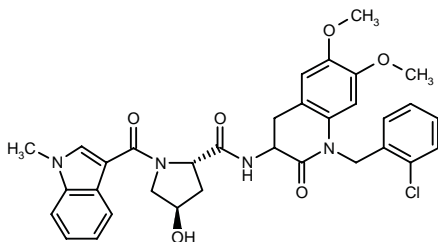
SOURCE – SmithKline Beecham.

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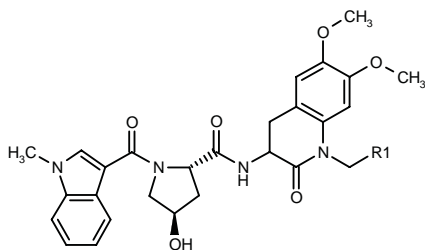
259398

N-[1-(2-Chlorobenzyl)-6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-4(*R*)-hydroxy-1-(1-methylindol-3-ylcarbonyl)-L-prolinamide



C33-H33-Cl-N4-O6; Mol wt: 617.10

ACTION – Tachykinin antagonist with particularly good activity against substance P, but also against neurokinin A and neurokinin B. Compound inhibited [125 I]-substance P binding in human lymphoblastoma IM-9 cells with cloned NK_1 receptors with an IC_{50} value of 0.4 nM. Potentially useful for the treatment or prevention of neurokinin-mediated diseases such as asthma, bronchitis, rhinitis, conjunctivitis, dermatitis, urticaria, arthritis, irritable colon, vomiting, pain and migraine. A representative compound from a series of amino acid derivatives, wherein the following are also included:



Compound	R1	Formula
259561	2-Br-Ph	$C_{33}H_{33}BrN_4O_6$
259562	2-F-Ph	$C_{33}H_{33}FN_4O_6$
259563	2-Et-Ph	$C_{35}H_{38}N_4O_6$
259565	2,3-(Cl)2-Ph	$C_{33}H_{32}Cl_2N_4O_6$
259566	2,4-(Cl)2-Ph	$C_{33}H_{32}Cl_2N_4O_6$
259567	(F)5-Ph	$C_{33}H_{29}F_5N_4O_6$

SOURCE – Boehringer Ingelheim.

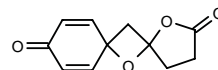
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BM-16.2115*

205571

1,6-Dioxadispiro[4.1.5.1]trideca-8,11-diene-2,10-dione



C11-H10-O4; Mol wt: 206.20

ACTION – Phospholipase A_2 (PLA $_2$) inhibitor shown to concentration-dependently inhibit the fMLP-stimulated chemotaxis of mixed human lymphocytes at 0.5-50 μ mol/l, being about 2-fold more potent than the reference compounds mepacrine and manoalide; this effect was suggested to be due to a reduction in LTB $_4$ production. Potentially useful for the treatment of inflammatory disorders such as asthma, arthritis and psoriasis.

SOURCE – Boehringer Mannheim.

REFERENCES

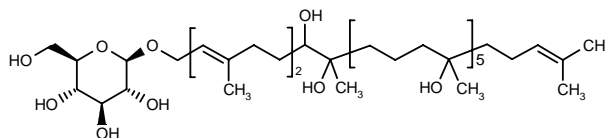
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2. Hinder, M. *Investigation on the effect of experimental phospholipase A2 inhibitors on the formyl-methionyl-leucyl-phenylalanine-stimulated chemotaxis of human leukocytes in vitro*. *Arzneim-Forsch-Drug Res* 1998, 48(1): 77.
3. Waldemar, A. et al. *Preparative UV-VIS laser photochemistry: Photocycloadditions of methylenelactones with benzophenone and p-benzoquinone. Oxygen trapping of Paterno-Buchi triplet 1,4-diradicals as model reactions for Quinghaosu-type 1,2,4-trioxanes*. *Liebigs Ann Chem* 1988, 9: 869.

*Identified compound **205571** Drug Data Rep 1994, 16(7): 621.

SCH-60059

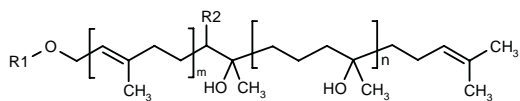
258353

(3*E*,34*E*)-36-(β -D-Glucopyranosyloxy)-2,6,10,14,18,22,26,30,34-nonamethyl-2,30,34-hexatriacontatriene-6,10,14,18,22,26,27-heptaol

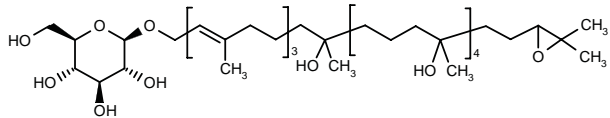


C51-H96-O13; Mol wt: 917.31

ACTION – Neurokinin (NK) receptor antagonist obtained from a fungal fermentation broth of *Acremonium* sp., with high affinity for both NK_1 ($IC_{50} = 3 \mu$ M for displacement of [prolyl-3,4- 3 H]-substance P binding in membranes from CHO cells expressing human NK_1 receptors) and NK_2 receptors ($IC_{50} = 11 \mu$ M for displacement of [4,5- 3 H-Leu 9]-NKA binding in membranes from CHO cells expressing human NK_2 receptors), giving an NK_2/NK_1 ratio of 3.7. Such compounds are thought to have potential utility in the treatment of inflammation, bronchoconstriction and pain. Other polyhydroxy-isoprenoids from the same source are:



Compound	R1	R2	m	n	Formula
Sch-60065 [258344]	β-D-glucopyranosyl	H	2	5	C ₅₁ H ₉₆ O ₁₂
Sch-60061 [258355]	H	H	2	5	C ₄₅ H ₈₆ O ₇
Sch-60063 [258356]	β-D-glucopyranosyl	H	3	4	C ₅₁ H ₉₄ O ₁₁
Sch-60057 [258357]	H	H	3	4	C ₄₅ H ₈₄ O ₆
Sch-66878 [258358]	H	OH	3	10	C ₇₅ H ₁₄₄ O ₁₃



Sch-64879 [258354]: C₅₁-H₉₄-O₁₂

SOURCE – Schering-Plough.

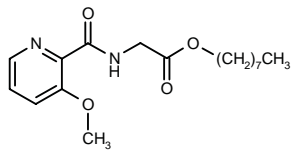
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TREATMENT OF RDS AND EMPHYSEMA

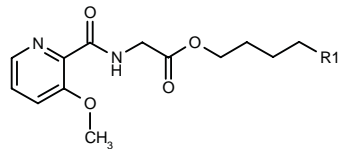
257762

N-(3-Methoxypyridin-2-ylcarbonyl)glycine octyl ester



C17-H26-N2-O4; Mol wt: 322.40

ACTION – Antifibrotic ester prodrug with more potent proline hydroxylase (prolyl-4-hydroxylase)- and collagen biosynthesis-inhibitory activity than structurally related compounds. Potentially useful for the treatment of fibrotic diseases of the lungs, liver, kidney, heart, eye and skin, and arteriosclerosis. Other exemplified compounds include the following:



Compound	R1	Formula
259603	H	C ₁₃ H ₁₈ N ₂ O ₄
259604	C8H17	C ₂₁ H ₃₄ N ₂ O ₄
259605	C11H23	C ₂₄ H ₄₀ N ₂ O ₄

SOURCE – Hoechst Marion Roussel.

REFERENCES

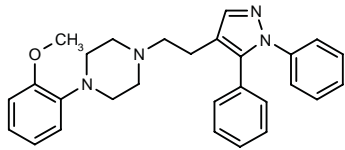
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

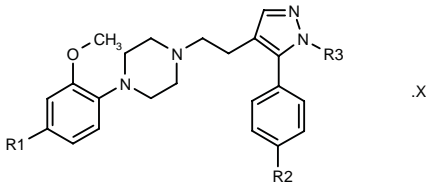
256472

4-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1,5-diphenylpyrazole



C28-H30-N4-O; Mol wt: 438.57

ACTION – α₁-Adrenoceptor antagonist (IC₅₀ = 1.1 nM against [³H]-prazosin binding in rat brain preparations), shown to inhibit phenylephrine-induced contractions of isolated dog prostate (pA₂ = 8.80 vs. 8.24 for prazosin). Potentially useful for the treatment of hypertension and urinary disorders. Other compounds from this series of pyrazole derivatives include the following:



Compound	R1	R2	R3	X	Formula
260372	H	F	Me		C ₂₃ H ₂₇ FN ₄ O
260373	H	OH	Me	2HCl	C ₂₃ H ₂₈ N ₄ O ₂ ·2HCl
260374	F	OH	CH ₂ CH ₂ OH	fumarate	C ₂₄ H ₂₉ FN ₄ O ₃ ·C ₄ H ₄ O ₄

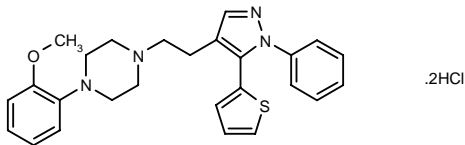
SOURCE – Taisho.

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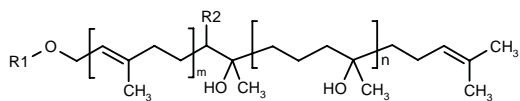
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256473

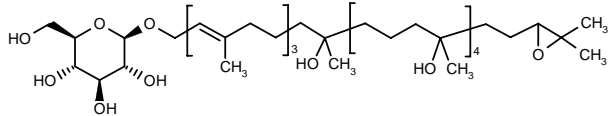
4-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-phenyl-5-(2-thienyl)pyrazole dihydrochloride



C26-H28-N4-O-S.2HCl; Mol wt: 517.52



Compound	R1	R2	m	n	Formula
Sch-60065 [258344]	β-D-glucopyranosyl	H	2	5	C ₅₁ H ₉₆ O ₁₂
Sch-60061 [258355]	H	H	2	5	C ₄₅ H ₈₆ O ₇
Sch-60063 [258356]	β-D-glucopyranosyl	H	3	4	C ₅₁ H ₉₄ O ₁₁
Sch-60057 [258357]	H	H	3	4	C ₄₅ H ₈₄ O ₆
Sch-66878 [258358]	H	OH	3	10	C ₇₅ H ₁₄₄ O ₁₃



Sch-64879 [258354]: C₅₁-H₉₄-O₁₂

SOURCE – Schering-Plough.

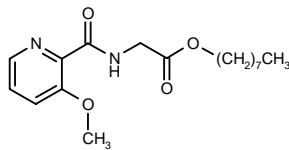
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TREATMENT OF RDS AND EMPHYSEMA

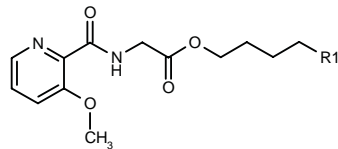
257762

N-(3-Methoxypyridin-2-ylcarbonyl)glycine octyl ester



C17-H26-N2-O4; Mol wt: 322.40

ACTION – Antifibrotic ester prodrug with more potent proline hydroxylase (prolyl-4-hydroxylase)- and collagen biosynthesis-inhibitory activity than structurally related compounds. Potentially useful for the treatment of fibrotic diseases of the lungs, liver, kidney, heart, eye and skin, and arteriosclerosis. Other exemplified compounds include the following:



Compound	R1	Formula
259603	H	C ₁₃ H ₁₈ N ₂ O ₄
259604	C8H17	C ₂₁ H ₃₄ N ₂ O ₄
259605	C11H23	C ₂₄ H ₄₀ N ₂ O ₄

SOURCE – Hoechst Marion Roussel.

REFERENCES

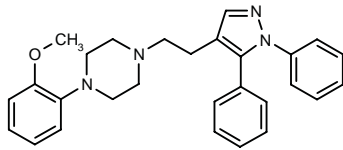
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

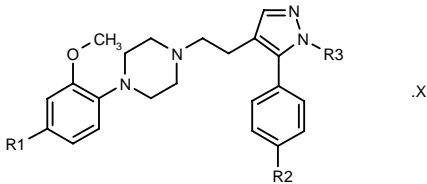
256472

4-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1,5-diphenylpyrazole



C28-H30-N4-O; Mol wt: 438.57

ACTION – α₁-Adrenoceptor antagonist (IC₅₀ = 1.1 nM against [³H]-prazosin binding in rat brain preparations), shown to inhibit phenylephrine-induced contractions of isolated dog prostate (pA₂ = 8.80 vs. 8.24 for prazosin). Potentially useful for the treatment of hypertension and urinary disorders. Other compounds from this series of pyrazole derivatives include the following:



Compound	R1	R2	R3	X	Formula
260372	H	F	Me		C ₂₃ H ₂₇ FN ₄ O
260373	H	OH	Me	2HCl	C ₂₃ H ₂₈ N ₄ O ₂ ·2HCl
260374	F	OH	CH ₂ CH ₂ OH	fumarate	C ₂₄ H ₂₉ FN ₄ O ₃ ·C ₄ H ₄ O ₄

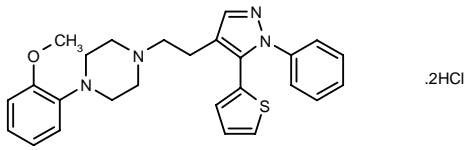
SOURCE – Taisho.

REFERENCES

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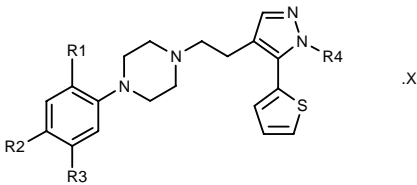
256473

4-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-1-phenyl-5-(2-thienyl)pyrazole dihydrochloride

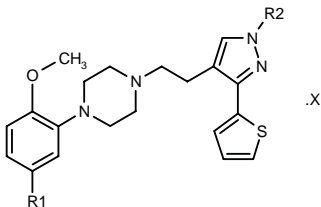


C26-H28-N4-O-S.2HCl; Mol wt: 517.52

ACTION – α_1 -Adrenoceptor antagonist (IC₅₀ = 6.7 nM against [³H]-prazosin binding in rat brain preparations vs. 741 nM for urapidil) with potential in the treatment of hypertension and urinary disorders. A representative compound from a series of thienylpyrazole derivatives, where- in the following are also included:



Compound	R1	R2	R3	R4	X	Formula
260380	OMe	H	H	2-Pyr		C ₂₅ H ₂₇ N ₅ OS
260381	OMe	H	H	4-F-Ph		C ₂₆ H ₂₇ FN ₄ OS
260383	OMe	H	H	H	2HCl	C ₂₀ H ₂₄ N ₄ O ₂ .2HCl
260382	Cl	H	H			C ₂₀ H ₂₃ ClN ₄ S
260384	OMe	H	H	Me	2HCl	C ₂₁ H ₂₆ N ₄ O ₂ .2HCl
260385	OMe	F	H	Me	2HCl	C ₂₁ H ₂₅ FN ₄ O ₂ .2HCl
260386	OMe	F	H	CH ₂ CH ₂ OH	3HCl	C ₂₂ H ₂₇ FN ₄ O ₂ S.3HCl
260388	OMe	H	Cl	Me	3HCl	C ₂₁ H ₂₅ ClN ₄ O ₂ .3HCl
260389	OMe	H	Cl	CH ₂ CH ₂ OH	3HCl	C ₂₂ H ₂₇ ClN ₄ O ₂ S.3HCl



Compound	R1	R2	X	Formula
260387	Cl	H	3HCl	C ₂₀ H ₂₃ ClN ₄ O ₂ .3HCl
260390	H	Me	2HCl	C ₂₁ H ₂₆ N ₄ O ₂ .2HCl

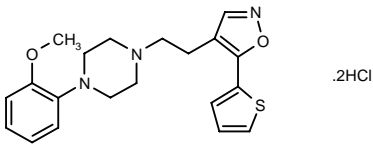
SOURCE – Taisho.

REFERENCES

1. Taguchi, M. et al. (Taisho Pharm. Co., Ltd.) *Thienylpyrazole derivs.* JP 97227555.

256474

4-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-5-(2-thienyl)isoxazole dihydrochloride



C20-H23-N3-O2-S.2HCl; Mol wt: 442.40

ACTION – α_1 -Adrenoceptor antagonist (IC₅₀ = 83.0 nM against [³H]-prazosin binding in rat brain preparations vs. 741 nM for urapidil) with potential in the treatment of hypertension and urinary disorders.

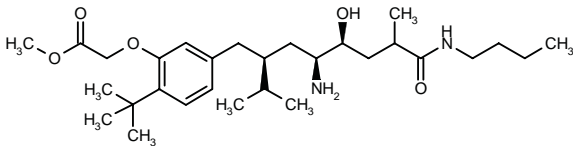
SOURCE – Taisho.

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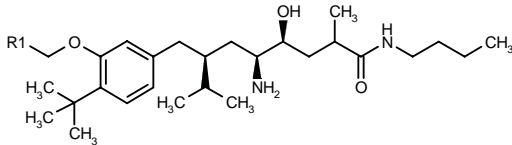
256885

(4*S*,5*S*,7*S*)-5-Amino-*N*-butyl-8-[4-*tert*-butyl-3-(methoxycarbonylmethoxy)phenyl]-4-hydroxy-7-isopropyl-2-methyloctanamide



C29-H50-N2-O5; Mol wt: 506.72

ACTION – Low-molecular-weight transition-state peptidomimetic renin inhibitor with high binding affinity for purified human renin (IC₅₀ = 6.0 nM, pH 7.2). Potentially useful for the treatment of hypertension and other cardiovascular diseases. Other 5(*S*)-amino-4(*S*)-hydroxy-8-phenyloctanecarboxamides with a similar profile are:



Compound	R1	Formula
256886	CONH2	C ₂₈ H ₄₉ N ₃ O ₄
256887	SO ₂ Me	C ₂₈ H ₅₀ N ₂ O ₅ S

SOURCE – Novartis.

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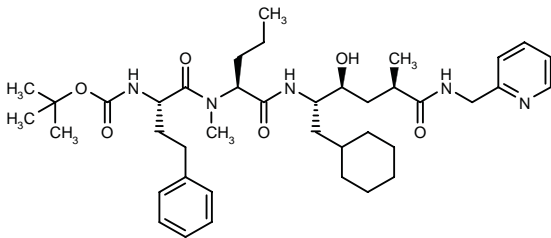
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2. Göschke, R. et al. *Design and synthesis of novel 2,7-dialkyl substituted 5(S)-amino-4(S)-hydroxy-8-phenyloctanecarboxamides as in vitro potent peptidomimetic inhibitors of human renin.* Bioorg Med Chem Lett 1997, 7(21): 2735.

259655

[3*S*-(3*R*^{*},6*R*^{*},9*R*^{*},10*R*^{*},12*S*^{*})]-9-(Cyclohexylmethyl)-10-hydroxy-5,12-dimethyl-4,7,13-trioxo-3-(2-phenylethyl)-6-propyl-15-(2-pyridinyl)-2,5,8,14-tetraazapentadecanoic acid *tert*-butyl ester

tert-Butoxycarbonyl-L-homophenyl-alanyl-2(*S*)-(N-methylamino)pentanoyl-3-cyclohexyl-L-alanyl-ψ[(*S*)-CH(OH)CH₂]-L-alanine (pyridin-2-ylmethyl)amide



C40-H61-N5-O6; Mol wt: 707.95

ACTION – Potent, specific, low-molecular-weight renin inhibitor (IC_{50} = 3.98 and 15.85 nM, respectively, for inhibition of trypsin-activated human plasma renin at pH 6.0 and 7.2) stable to degradation by α -chymotrypsin, proven to be orally available in rats. Potentially useful for the treatment of hypertension.

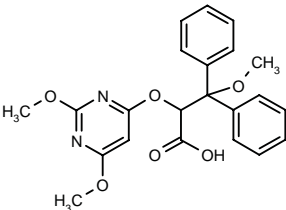
SOURCES – Astra; Ferring.

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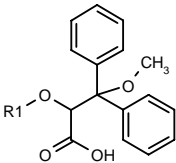
257247

2-(2,6-Dimethoxypyrimidin-4-yloxy)-3-methoxy-3,3-diphenylpropionic acid



C22-H22-N2-O6; Mol wt: 410.43

ACTION – Antihypertensive and antiischemic agent, an endothelin receptor antagonist showing selectivity for ET_A receptors over ET_B receptors (K_i = 0.038 and 8 μ M, respectively, using cloned human receptors). Other representative compounds within this series of carboxylic acid derivatives include the following:



Compound	R1	Formula
259570	2-t-Bu-6-CF3-4-pyrimidinyl	C ₂₅ H ₂₅ F ₃ N ₂ O ₄
259571	4-Me-2-quinolyl	C ₂₆ H ₂₃ NO ₄
259572	2-quinolinyl	C ₂₅ H ₂₁ NO ₄

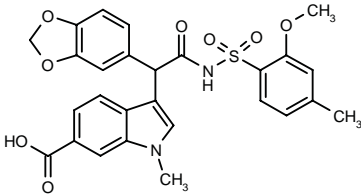
SOURCE – BASF.

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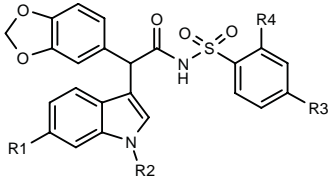
258983

3-[1-(1,3-Benzodioxol-5-yl)-2-(2-methoxy-4-methylphenyl-sulfonamido)-2-oxoethyl]-1-methylindole-6-carboxylic acid



C27-H24-N2-O8-S; Mol wt: 536.56

ACTION – Agent for the treatment of disorders including pulmonary hypertension, renal failure and restenosis with potent binding affinity for ET_A receptors (IC_{50} < 500 nM) and selectivity (> 100) for ET_A receptors over ET_B receptors. Other representative compounds within this series of indole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
259322	CONH2	Me	CH2CH2CO2H	H	C ₂₈ H ₂₅ N ₃ O ₈ S
259323	CH2OH	Me	Me	OMe	C ₂₇ H ₂₆ N ₂ O ₇ S
259324	F	Me	Me	OMe	C ₂₆ H ₂₃ FN ₂ O ₆ S
259325	Ac	Me	Me	OMe	C ₂₈ H ₂₆ N ₂ O ₇ S
259326	CONH2	CH2CH2OMe	Me	OMe	C ₂₉ H ₂₉ N ₃ O ₈ S

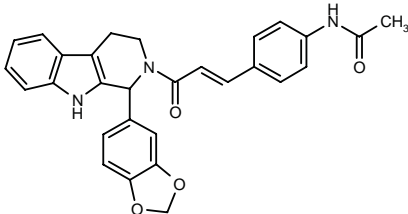
SOURCE – Pfizer.

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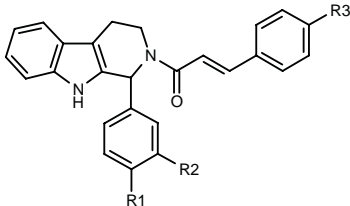
258999

N-[4-[3-[1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-yl]-3-oxo-1(E)-propenyl]phenyl]-acetamide



C29-H25-N3-O4; Mol wt: 479.53

ACTION – Agent for the treatment of cardiovascular disorders, a potent and selective inhibitor of cGMP phosphodiesterase (IC_{50} = 5 nM using human PDE V), proven to stimulate the accumulation of cGMP in rat aortic smooth muscle cells (EC_{50} = 0.45 μ M). Significant hypotensive activity was observed in conscious spontaneously hypertensive rats at a dose of 5 mg/kg p.o. Other compounds from this series of carboline derivatives include the following:



Compound	R1,R2	R3	Isomer	Formula
260039	-OCH2O-	NO2		C ₂₇ H ₂₁ N ₃ O ₅
260040	-OCH2O-	CO2Me		C ₂₉ H ₂₄ N ₂ O ₅
260041	-OCH2CH2-	OCH2CH2N(Me)2	R	C ₃₂ H ₃₃ N ₃ O ₃
260042	-OCH2CH2-	OCH2CH(OH)CH2N(Me)2	R	C ₃₃ H ₃₅ N ₃ O ₄

SOURCE – Icos.

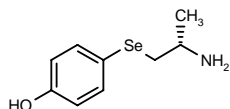
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1. Bombrun, A. (Icos Corp.) *Carboline derivs.* WO 9743287.

HOMePAESe

259857

(S)-4-(2-Aminopropylselanyl)phenol



C9-H13-N-O-Se; Mol wt: 230.17

M.p. 180 °C (decomp.).

ACTION – The first orally active, selenium-based antihypertensive agent. It exhibits both restricted CNS permeability and marked oral antihypertensive activity in spontaneously hypertensive rats (100-200 mg/kg p.o.).

SOURCES – Georgia Inst. Technol., Atlanta, GA (US); Mercer Univ., Atlanta, GA (US).

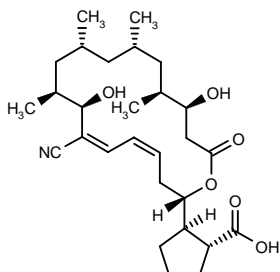
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

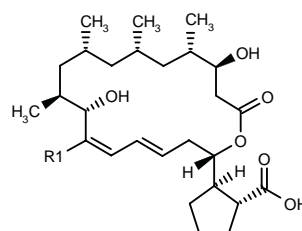
256434

(2S,4Z,6Z,8R,9S,11R,13S,15S,16S)-2(R)-(7-Cyano-8,16-dihydroxy-9,11,13,15-tetramethyl-18-oxooxacyclo-octadeca-4,6-dien-2-yl)cyclopentane-1(R)-carboxylic acid



C28-H43-N-O6; Mol wt: 489.65

ACTION – Antiangiogenic agent that inhibits abnormal proliferation of vascular tissues, e.g., in atherosclerosis, rheumatoid arthritis, cancer and diabetic retinopathy, obtained by culturing the microorganism *Streptomyces rochei* Mer N-7167, giving an IC₅₀ value of 4.4 ng/ml when assessed for its ability to inhibit the formation of new blood vessels around excised rat aorta preparations. Other exemplified compounds include the following:



Compound	R1	Formula
260420	CN	C ₂₈ H ₄₃ NO ₆
260421	CO ₂ H	C ₂₈ H ₄₄ O ₈

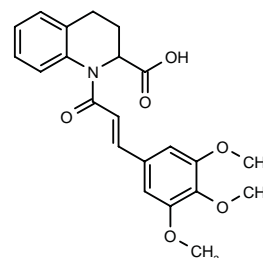
SOURCES – Eisai; Mercian.

REFERENCES

1. Wakabayashi, T. et al. (Mercian Corp.; Eisai Co., Ltd.) *Novel biogenic substances.* JP 97227549.

256466

1-(3,4,5-Trimethoxycinnamoyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid



C22-H23-N-O6; Mol wt: 397.43

ACTION – Agent for the treatment of restenosis, an inhibitor of vascular smooth muscle cell proliferation, as demonstrated against aortic smooth muscle cells isolated from spontaneously hypertensive rats (IC₅₀ = 32 μM).

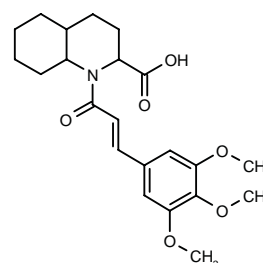
SOURCE – Kissei.

REFERENCES

1. Harada, H. et al. (Kissei Pharm. Co., Ltd.) *Tetrahydroquinolincarbonate derivs.* JP 97255660.

256479

1-(3,4,5-Trimethoxycinnamoyl)perhydroquinoline-2-carboxylic acid



C22-H29-N-O6; Mol wt: 403.47

ACTION – Agent for the treatment of restenosis, an inhibitor of vascular smooth muscle cell proliferation, as demonstrated against aortic smooth muscle cells isolated from spontaneously hypertensive rats (IC_{50} = 104 μ M).

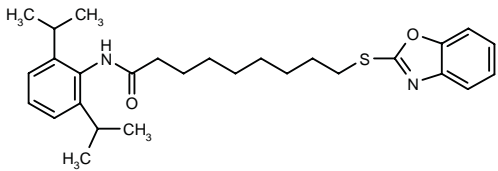
SOURCE – Kissei.

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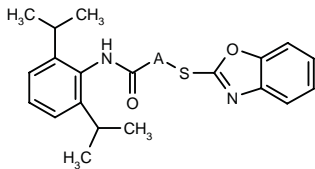
258593

9-(Benzoxazol-2-ylsulfanyl)-N-(2,6-diisopropylphenyl)-nonanamide



C28-H38-N2-O2-S; Mol wt: 466.68

ACTION – Antiatherosclerotic agent, an ACAT inhibitor that shows selectivity for a subtype of the enzyme present in blood vessel wall (IC_{50} = 0.004 μ M using rabbit enzyme) as compared to the subtype from small intestine (IC_{50} = 0.021 μ M using rabbit enzyme). *In vivo*, it markedly inhibited the increase in total plasma cholesterol in hamsters when added at concentrations of 0.03-0.3% to a high-fat diet (80.5-111.7% inhibition after 4 weeks of treatment). Antifoaming activity was determined by measuring ACAT inhibition in J774 cells (IC_{50} = 0.007 μ M) and HepG2 cells (IC_{50} = 0.61 μ M; ratio HepG2/J774 = 87.14). Within this series of anilide derivatives, the following are also included:



Compound	A	Formula
259307	-(CH2)-	C ₂₁ H ₂₄ N ₂ O ₂ S
259308	-(CH2)2-	C ₂₂ H ₂₆ N ₂ O ₂ S
259309	-(CH2)3-	C ₂₃ H ₂₈ N ₂ O ₂ S
259310	-(CH2)5-	C ₂₅ H ₃₂ N ₂ O ₂ S
259311	-(CH2)6-	C ₂₆ H ₃₄ N ₂ O ₂ S

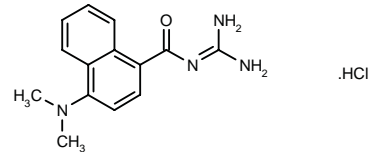
SOURCE – Kowa.

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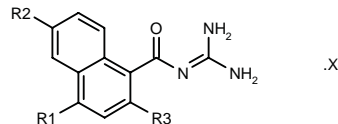
258707

N²-[4-(Dimethylamino)-1-naphthoyl]guanidine hydrochloride



C14-H16-N4-O.HCl; Mol wt: 292.77

ACTION – Antiarrhythmic agent with cardioprotective activity that acts by inhibiting Na⁺/H⁺ exchange, as demonstrated in an *in vitro* assay using dog erythrocytes (IC_{50} = 0.2 μ M). Potentially useful for the treatment or prevention of myocardial infarction, angina pectoris, cardiac and cerebral ischemic disorders, etc. Within this series of substituted 1-naphthoylguanidines, the following are also included:



Compound	R1	R2	R3	X	Formula
259611	F	H	H	HCl	C ₁₂ H ₁₀ FN ₃ O.HCl
259612	H	OCH2CH2N(Et)2	H		C ₁₈ H ₂₄ N ₄ O ₂
259613	H	H	H	HCl	C ₁₂ H ₁₁ N ₃ O.HCl
259614	H	H	OMe	HCl	C ₁₃ H ₁₃ N ₃ O ₂ .HCl
259615	H	H	OBu	HCl	C ₁₆ H ₁₉ N ₃ O ₂ .HCl
259616	H	H	i-PrO	HCl	C ₁₅ H ₁₇ N ₃ O ₂ .HCl
259617	H	H	OCH2Ph	HCl	C ₁₉ H ₁₇ N ₃ O ₂ .HCl

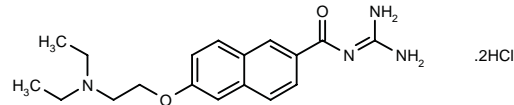
SOURCE – Hoechst Marion Roussel.

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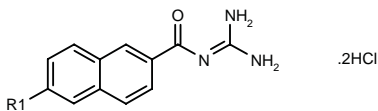
258708

N²-[6-[2-(Diethylamino)ethoxy]-2-naphthoyl]guanidine dihydrochloride

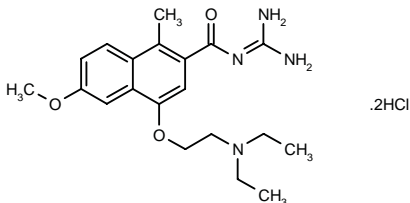


C18-H24-N4-O2.2HCl; Mol wt: 401.34

ACTION – Antiarrhythmic agent with cardioprotective activity that acts by inhibiting Na⁺/H⁺ exchange, as demonstrated *in vitro* in dog erythrocytes. Potentially useful for the treatment or prevention of myocardial infarction, angina pectoris, cardiac and cerebral ischemic disorders, etc. Other exemplified substituted 2-naphthoylguanidines include the following:



Compound	R1	Formula
259675	OCH2CH2N(i-Pr)2	C ₂₀ H ₂₈ N ₄ O ₂ ·2HCl
259676	4-morpholinyl-CH2CH2O	C ₁₈ H ₂₂ N ₄ O ₃ ·2HCl
259677	OCH2CON=C(NH2)2	C ₁₅ H ₁₆ N ₆ O ₃ ·2HCl
259678	3-Pyr-CH2NHCO	C ₁₉ H ₁₇ N ₅ O ₂ ·2HCl
259679	CONHCH2CH2OCON=C(NH2)2	C ₁₇ H ₁₉ N ₇ O ₄ ·2HCl
259680	4-(4-Cl-Ph)-1-Piz-CH2CH2O	C ₂₄ H ₂₆ Cl ₂ N ₅ O ₂ ·2HCl



259681: C₂₀-H₂₈-N₄-O₃·2HCl

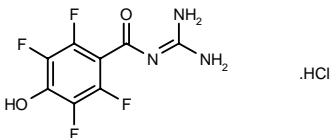
SOURCE – Hoechst Marion Roussel.

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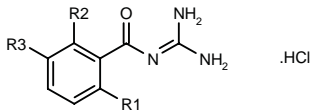
258709

*N*²-(2,3,5,6-Tetrafluoro-4-hydroxybenzoyl)guanidine hydrochloride



C₈-H₅-F₄-N₃-O₂·HCl; Mol wt: 287.60

ACTION – Antiarrhythmic agent with cardioprotective properties that acts by inhibiting Na⁺/H⁺ exchange, as demonstrated *in vitro* in dog erythrocytes (IC₅₀ = 0.3 μM). Potentially useful for the treatment or prevention of myocardial infarction, angina pectoris, cardiac and cerebral ischemic disorders, etc. Other representative compounds within this series of bis-ortho-substituted benzoylguanidines include the following:



Compound	R1	R2	R3	Formula
259682	OMe	OMe	Cl	C ₁₀ H ₁₂ ClN ₃ O ₃ ·HCl
259683	F	F	H	C ₈ H ₇ F ₂ N ₃ O ₃ ·HCl
259684	CF3	F	H	C ₉ H ₇ F ₄ N ₃ O ₃ ·HCl
259685	OMe	OMe	CF3	C ₁₁ H ₁₂ F ₃ N ₃ O ₃ ·HCl

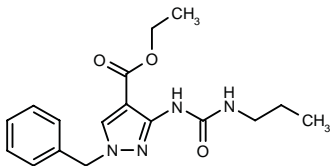
SOURCE – Hoechst Marion Roussel.

REFERENCES

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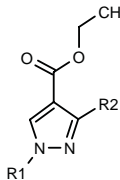
258711

1-Benzyl-3-(3-propylureido)pyrazole-4-carboxylic acid ethyl ester



C₁₇-H₂₂-N₄-O₃; Mol wt: 330.39

ACTION – Smooth muscle cell proliferation inhibitor for the treatment or prevention of restenosis following percutaneous transluminal coronary angioplasty (PTCA), as well as membrane proliferative nephritis, arterio-sclerotic diseases, hypertension or diabetes mellitus. It inhibited platelet-derived growth factor (PDGF)-stimulated fibroblast growth by 84.5% at 3 μM, without inhibiting cell growth in the absence of growth factors such as PDGF at concentrations of 0.1 mM or less; it also inhibited PDGF-stimulated human coronary artery smooth muscle cell growth, with an IC₅₀ of 2.3 μM. Within this series of pyrazole derivatives, the following are also included:



Compound	R1	R2	Formula
259134	Bu	NHCONHPh	C ₁₇ H ₂₂ N ₄ O ₃
259135	Bu	NHCSNHPh	C ₁₇ H ₂₂ N ₄ O ₂ S
259136	Ph	H	C ₁₉ H ₁₈ N ₄ O ₃
259137	Ph	H	C ₁₆ H ₂₀ N ₄ O ₃
259138	CH2Ph	i-Pr-NHCONH	C ₁₇ H ₂₂ N ₄ O ₃
259139	CH2Ph	NHCON(Pr)2	C ₂₀ H ₂₈ N ₄ O ₃
259140	CH2Ph	NHCON(Ph)2	C ₂₆ H ₂₄ N ₄ O ₃
259141	CH2Ph	N(CH2Ph)CONHPh	C ₂₇ H ₂₆ N ₄ O ₃

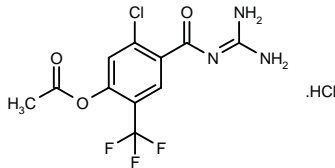
SOURCE – Japan Energy.

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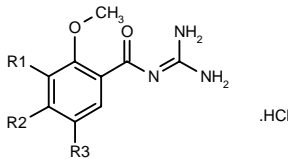
258720

*N*²-[4-Acetoxy-2-chloro-5-(trifluoromethyl)benzoyl]-guanine hydrochloride



C11-H9-Cl-F3-N3-O3.HCl; Mol wt: 360.12

ACTION – Antiarrhythmic agent with cardioprotective properties for the treatment or prevention of ischemic disorders that acts by inhibiting Na⁺/H⁺ exchange. Other exemplified *ortho*-substituted benzoylguanidines include the following:



Compound	R1	R2	R3	Formula
259686	H	OAc	CF3	C ₁₂ H ₁₂ F ₃ N ₃ O ₄ .HCl
259687	OAc	H	t-Bu	C ₁₅ H ₂₁ N ₃ O ₄ .HCl

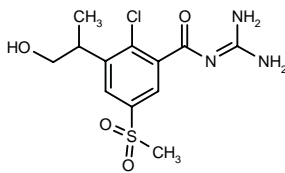
SOURCE – Hoechst Marion Roussel.

REFERENCES

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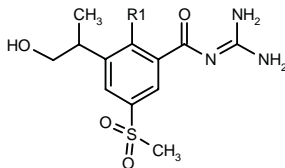
258741

*N*²-[2-Chloro-3-(2-hydroxy-1-methylethyl)-5-(methylsulfonyl)benzoyl]guanidine



C12-H16-Cl-N3-O4-S; Mol wt: 333.79

ACTION – Antiarrhythmic agent with cardioprotective properties for the treatment or prevention of ischemic disorders that acts by inhibiting Na⁺/H⁺ exchange, as demonstrated in *in vitro* studies in dog erythrocytes (IC₅₀ < 10 μM). Other exemplified benzoylguanidines include the following:



Compound	R1	Formula
259688	OMe	C ₁₃ H ₁₉ N ₃ O ₅ S
259689	Me	C ₁₃ H ₁₉ N ₃ O ₄ S

SOURCE – Hoechst Marion Roussel.

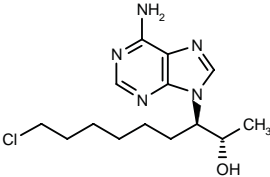
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1. Weichert, A. et al. (Hoechst AG) *Benzoylguanidines, process for their preparation and medicaments containing them.* EP 814077.

CPC-405

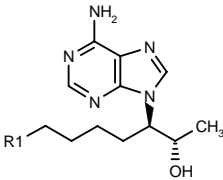
259848

9-[1(*R*)-(6-Chlorohexyl)-2(*S*)-hydroxypropyl]adenine



C14-H22-Cl-N5-O; Mol wt: 311.81

ACTION – Specific, reversible, small-molecule adenosine deaminase inhibitor that increases the levels of adenosine. Title compound was able to inhibit adenosine deaminase in cell-free preparations (K_i = 2.7 nM against purified calf spleen enzyme) and in intact cells (IC₅₀ = 2.61 ± 0.5 and 0.22 ± 0.1 μM in human astrocytoma and red blood cells, respectively), without affecting adenosine transport or adenosine kinase activity. CPC-405 increased adenosine release from human astrocytoma cells and bovine heart microvascular endothelial cells, and it exhibited cardioprotective properties in the isolated ischemic rat heart. This agent may represent a new class of compounds with clinical utility in a range of ischemic disorders such as cardiovascular and cerebrovascular ischemia. Other related *erythro*-9-(2-hydroxy-3-nonyl)-adenine (EHNA) analogs are:



Compound	R1	Formula
CPC-402* [234244]	CH2CH2OH	C ₁₄ H ₂₃ N ₅ O ₂
CPC-406 [259850]	1,3-dioxo-2-isindolyl-CH2CH2	C ₂₂ H ₂₆ N ₆ O ₃
CPC-407 [259851]	vinyl	C ₁₄ H ₂₁ N ₅ O
CPC-410 [259852]	CH2CH2OSi(t-Bu)(Ph) ₂	C ₃₀ H ₄₁ N ₅ O ₂ Si

SOURCE – Cypros.

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4. Cypros Pharmaceutical Corp. Annual Report 1993.

*Identified compound 234244 Drug Data Rep 1996, 18(5): 427.

PANTARIN™

230568

Basic fibroblast growth factor (FGF2) conjugated to saporin (ribosome-inactivating protein derived from the plant Saponaria officinalis)

FGF2-SAP
FGF-SAP

ACTION – Genetically engineered fusion protein that is a potent recombinant mitotoxin composed of the ribosome-inactivating protein saporin (SAP) and the mitogen basic fibroblast growth factor (FGF2); it selectively kills proliferating cells with upregulated FGF receptors. The mitotoxin was cytotoxic to cultured rat aortic smooth muscle cells (SMCs) at concentrations as low as 1 nmol/l, depending on incubation time, and it was shown to significantly inhibit neointimal formation in a rat model of carotid artery balloon injury when given systemically, as well as in dog models of intimal hyperplasia when given by local infusion; local administration minimizes the risk of side effects, particularly liver toxicity. It thus appears to be useful as a targeted therapy for reducing intimal hyperplasia. The fusion protein also exerts antitumor activity *in vitro* and *in vivo*, as shown against murine B16 melanoma, and appears to have potential for preventing posterior capsule opacification after cataract surgery.

SOURCES – Pharmacia & Upjohn; Prizim.

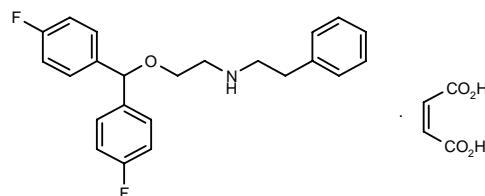
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19. *Update on Prizm's novel Directin-based product pipeline*. Prous Science Daily Essentials November 20, 1997.

VUF-8929

258874

N-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-*N*-(2-phenylethyl)amine maleate



C23-H23-F2-N-O.C4-H4-O4; Mol wt: 483.51

M.p. 145-7 °C.

ACTION – Voltage-dependent Ca^{2+} channel blocker proven to displace [^3H]-nitrendipine binding in cerebral cortex with a pK_D value of 6.27, and calmodulin antagonist ($\text{IC}_{50} = 4.3 \mu\text{mol/l}$ for inhibition of calmodulin-induced activation of phosphodiesterase); it inhibited both K^+ - and noradrenaline-induced contractions of rabbit aortic rings with IC_{50} values of 0.5 and $1.3 \mu\text{mol/l}$, respectively. The compound also exhibited affinity ($K_i = 6.63 \text{ nM}$) for the vesicular transporter for dopamine, as shown in rat striatal membranes using [^3H]-tyramine as ligand. VUF-8929 had antiischemic properties in dogs, both reducing the workload of the heart and increasing coronary blood flow after i.v. administration to anesthetized dogs at a dose of 0.3 mg/kg or more. In a canine model of cardiac ischemia induced by coronary artery ligation, VUF-8929 reduced epicardial and endocardial S-T segment elevation (40 and 30%, respectively), as well as local venous acidosis (50%), after a dose of 0.3 mg/kg i.v. However, similar to other diphenylalkylamines, VUF-8929 is highly lipophilic and strongly binds to plasma proteins, resulting in decreased efficacy when administered orally. Potentially useful for the treatment of angina pectoris and myocardial ischemia.

SOURCES – Organon; Vrije Univ., Amsterdam (NL).

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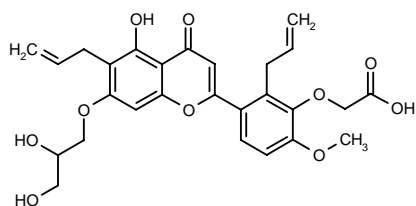
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MISCELLANEOUS CARDIOVASCULAR DRUGS

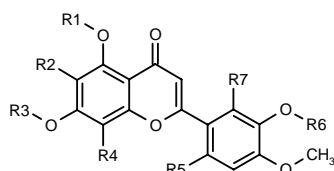
258580

2-[2-Allyl-3-[6-allyl-7-(2,3-dihydroxypropoxy)-5-hydroxy-4-oxo-4*H*-1-benzopyran-2-yl]-6-methoxyphenoxy]acetic acid



C27-H28-O10; Mol wt: 512.51

ACTION – Agent for the treatment of venous insufficiency with antihyperpermeability activity, a derivative of diosmetin. It was shown to inhibit histamine-induced extravasation in the hamster cheek pouch microcirculation at 100 mg/kg p.o. Other compounds from this series of diosmetin acids and esters include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
259429	H	H	CH ₂ CO ₂ H	H	H	Pr	H	C ₂₁ H ₂₀ O ₈
259430	H	H	CH ₂ CO ₂ H	H	H	H	allyl	C ₂₁ H ₁₈ O ₈
259431	CH ₂ -CO ₂ H	H	CH ₂ CO ₂ H	H	H	H	allyl	C ₂₃ H ₂₀ O ₁₀
259432	CH ₂ -CO ₂ H	H	CH ₂ CO ₂ H	H	H	H	Pr	C ₂₃ H ₂₂ O ₁₀
259433	CH ₂ -CO ₂ H	H	CH ₂ CO ₂ H	H	H	CH ₂ CO ₂ H	H	C ₂₂ H ₁₈ O ₁₂
259434	H	H	H	allyl	H	CH ₂ CO ₂ H	H	C ₂₁ H ₁₈ O ₈
259435	H	allyl	H	allyl	H	CH ₂ CO ₂ H	H	C ₂₄ H ₂₂ O ₈
259436	H	H	CH ₂ CO ₂ H	H	i-BuCH ₂	H	H	C ₂₃ H ₂₄ O ₈
259437	H	H	CH ₂ CH(OH)-CH ₂ OH	H	H	CH ₂ CO ₂ H	H	C ₂₁ H ₂₀ O ₁₀
259438	CH ₂ -CO ₂ H	H	CH ₂ CH(OH)-CH ₂ OH	H	H	CH ₂ CO ₂ H	Pr	C ₂₆ H ₂₈ O ₁₂

SOURCE – ADIR.

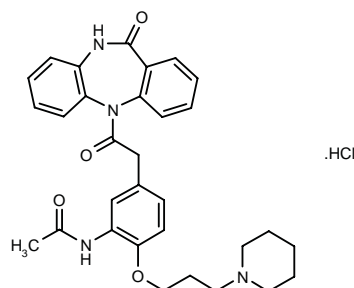
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YM-59981

259711

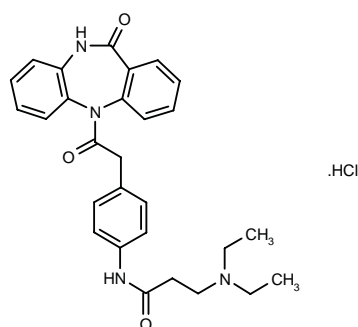
N-[5-[2-(11-Oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]-diazepin-5-yl)-2-oxoethyl]-2-[3-(1-piperidiny)propoxy]-phenyl]acetamide hydrochloride



C31-H34-N4-O4.HCl; Mol wt: 563.09

Colorless needles, m.p. 234-6 °C.

ACTION – Potent and selective muscarinic M₂ receptor antagonist, as demonstrated in binding assays by pK_i values of 8.1, 8.7 and 6.9 for M₁, M₂ and M₃ receptors, respectively (selectivity ratio M₁/M₂ = 4.0; M₃/M₂ = 63). *In vivo*, compound inhibited the oxotremorine-induced bradycardia (M₂) in pithed rats after i.v. (pDR₁₀ = 7.16) and p.o. administration (pDR₁₀ = 5.21), being slightly more potent than atropine (pDR₁₀ = 6.94 i.v.), whereas it showed much weaker inhibitory activity against oxotremorine-induced salivation in rats (pID₅₀ = 5.00 i.v.; M₃/M₂ = 288). It was about 3-fold more potent than AF-DX-116 in increasing heart rate in dogs with nocturnal bradycardia after oral administration. Compound was found to exhibit poor blood–brain penetration, as indicated by its lack of effect on oxotremorine-induced tremor in mice. Potentially useful for the treatment of functional sinus disorders such as sick sinus syndrome, with a low liability for side effects. Another related succinamide-type compound is:



YM-55758 [259712]: C28-H30-N4-O3.HCl

SOURCE – Yamanouchi.

REFERENCES

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2. Kakefuda, A. et al. *Synthesis and structure-activity relationships of novel antagonists for muscarinic M₂ receptors containing tricyclic ring skelton.* 16th Symp Med Chem (Nov 27-29, Toyama) 1996, Abst 1-P-8.

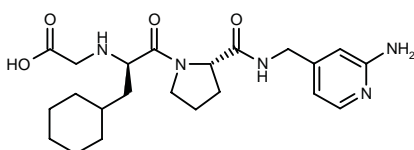
3. Watanabe, T. et al. *Synthesis and biological evaluation of phenylacetyl derivatives having low central nervous system permeability as potent and selective M₂ muscarinic receptor antagonists.* Chem Pharm Bull 1998, 46(1): 53.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

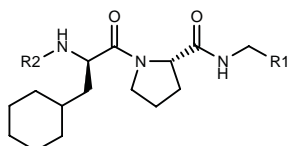
258780

N-(Carboxymethyl)-D-cyclohexylalanyl-L-proline 2-amino-pyridin-4-ylmethylamide



C22-H33-N5-O4; Mol wt: 431.53

ACTION – Anticoagulant and antithrombotic agent, a potent thrombin inhibitor proven to double the thrombin time (TT), activated partial thromboplastin time (APTT) and prothrombin time (PT) in human plasma at 21, 340 and 330 ng/ml, respectively. Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
259120	6-NH2-3-Pyr	CH2CO2H	C ₂₂ H ₃₃ N ₅ O ₄
259121	2-NH2-4-Pyr-CH2	CH2CO2H	C ₂₃ H ₃₅ N ₅ O ₄
259122	4-NH2-3-F-Ph	CH2CO2H	C ₂₃ H ₃₃ FN ₅ O ₄
259123	2-NH2-4-Pyr	SO2Et	C ₂₂ H ₃₅ N ₅ O ₄ S
259124	6-NH2-3-Pyr	SO2Et	C ₂₂ H ₃₅ N ₅ O ₄ S

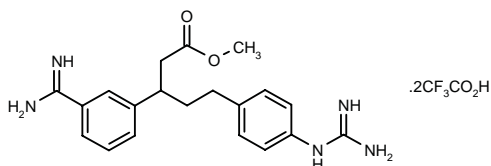
SOURCE – Lilly.

REFERENCES

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259294

(±)-3-(3-Amidinophenyl)-5-(4-guanidinophenyl)pentanoic acid methyl ester bistrifluoroacetate



C20-H25-N5-O2.2C2-H-F3-O2; Mol wt: 595.50

ACTION – Potent and specific factor Xa inhibitor ($K_i = 9$ nM) from a series of novel bis-phenylamidine carboxylate compounds; it shows 400-fold selectivity versus thrombin

($K_i = 3100$ nM) and 10-fold selectivity versus trypsin ($K_i = 96$ nM). Potentially useful as an antithrombotic agent.

SOURCE – DuPont Merck.

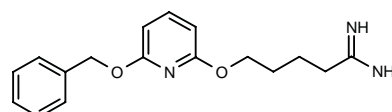
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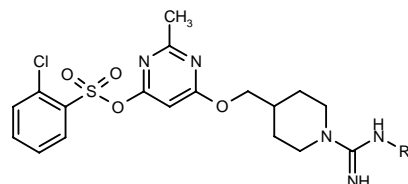
260090

5-(6-Benzyloxypyridin-2-yloxy)pentanamidine

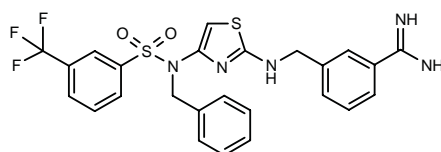


C17-H21-N3-O2; Mol wt: 299.37

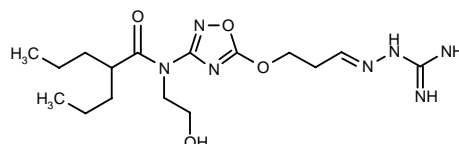
ACTION – Nonpeptide inhibitor of serine proteases, particularly trypsin-like serine proteases such as thrombin, plasmin, factor Xa, chymotrypsin and trypsin. A representative compound from a series of specifically claimed amidino and guanidino heterocyclic protease inhibitors claimed for use in the treatment of thrombosis, pancreatitis, ischemia, stroke, restenosis, emphysema and inflammation, wherein the following are also included:



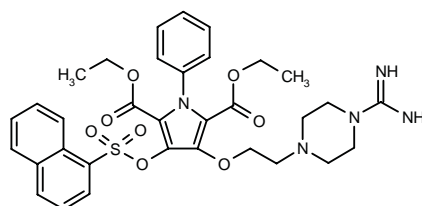
Compound	R1	Formula
260721	H	C ₁₈ H ₂₂ ClN ₅ O ₄ S
260722	5-Me-2-oxo-1,3-dioxol-4-yl-CH2OCO	C ₂₄ H ₂₆ ClN ₅ O ₉ S



260723: C25-H22-F3-N5-O2-S2



260724: C16-H29-N7-O4



260725: C33-H37-N5-O8-S

SOURCE – 3-Dimensional Pharm.

REFERENCES

1. Illig, C.R. et al. (3-Dimensional Pharm., Inc.) *Amidino and guanidino heterocyclic protease inhibitors*. WO 9747299.

KRAD-14

259011

Lysyl-alanyl-glutaminyl-tyrosyl-lysyl-lysyl-asparaginyl-lysyl-histidyl-arginyl-histidyl-seryl-isoleucyl-threonine

C76-H127-N27-O20; Mol wt: 1739.01

ACTION – Anticoagulant peptide derived from apolipoprotein B-100 (apo B-100) that has much higher activity than apo B-100 itself. Compound appears to inhibit the prothrombinase complex (factor Xa and factor V) in activating thrombin; it also prevents the activation of factor VII on the surface of thromboplastin, and it appears to affect the activation of platelets by thrombin.

SOURCE – Royal Free Hosp. School Med., London (GB).

REFERENCES

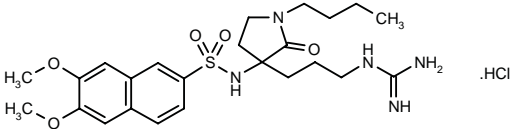
1. Bruckdorfer, K.R. and Ettelaie, C. (Royal Free Hosp. School Med.) *Anticoagulant peptide fragments derived from apolipoprotein B-100*. WO 9743311.

SPI-501*

256879

228502 (as free base)

N-[1-Butyl-3-(3-guanidinopropyl)-2-oxopyrrolidin-3-yl]-6,7-dimethoxynaphthalene-2-sulfonamide hydrochloride



C24-H35-N5-O5-S.HCl; Mol wt: 542.09

ACTION – Potent and highly selective thrombin inhibitor ($IC_{50} = 0.70 \mu M$, $K_i = 0.27 \mu M$ for human α -thrombin) with no inhibitory activity against other trypsin-like serine proteases ($IC_{50} > 100 \mu M$ for trypsin, factor Xa, plasmin and kallikrein). The compound doubled the thrombin-induced coagulation time in rabbit plasma ($1.7 \mu mol/l$) and the activated partial thromboplastin time (APTT) and prothrombin time (PT) in rat plasma (38.0 and $18.5 \mu mol/l$, respectively). Similar effects were also observed in *ex vivo* assays in rats after i.v. administration. SPI-501 is undergoing further evaluation for its potential in thrombosis prevention.

SOURCE – Fuji Chem.

REFERENCES

1. Okayama, T. et al. (Fuji Yakuhin Kogyo Co., Ltd.) *Lactam derivs. and their salts*. JP 97165370.

2. Okayama, T. et al. *Synthesis and antithrombin activity of lactam-conformationally restricted arginine derivatives*. 16th Symp Med Chem (Nov 27-29, Toyama) 1996, Abst 1-P-31.

3. Okayama, T. et al. *Anticoagulant activity of the novel thrombin inhibitor 1-butyl-3-(6,7-dimethoxy-2-naphthylsulfonyl)amino-3-(3-guanidinopropyl)-2-pyrrolidine hydrochloride*. *Arzneim-Forsch-Drug Res* 1997, 47(9): 1023.

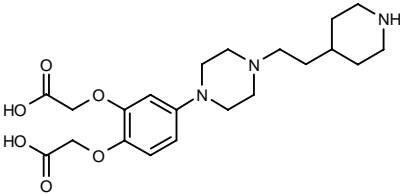
4. Okayama, T. et al. *Lactam-conformationally restricted analogs of N^ε-arylsulfonyl arginine amide: Design, synthesis and inhibitory activity toward thrombin and related enzymes*. *Chem Pharm Bull* 1995, 43(10): 1683.

*Identified compound **228502** Drug Data Rep 1996, 18(2): 145.

ANTIPLATELET THERAPY

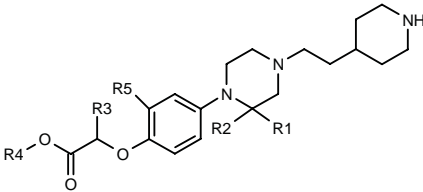
257208

2,2'-[4-[2-(4-Piperidyl)ethyl]piperazin-1-yl]phenylene-1,2-dioxy]bis(acetic acid)

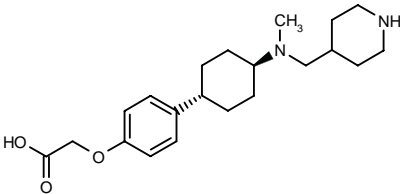


C21-H31-N3-O6; Mol wt: 421.49

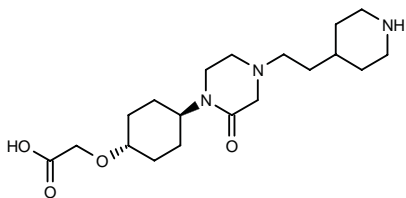
ACTION – Platelet aggregation inhibitor, a fibrinogen (gplIb/IIIa) antagonist proven to potently inhibit the binding of [3H]-BIBU-52 in human platelets ($IC_{50} = 47 \text{ nM}$) and collagen-induced human platelet aggregation ($EC_{50} = 110 \text{ nM}$). Other specifically claimed carboxylic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
259086	H	H	H	H	H	C ₁₉ H ₂₉ N ₃ O ₃
259087	-O-		H	H	H	C ₁₉ H ₂₇ N ₃ O ₄
259088	Me	H	H	H	H	C ₂₀ H ₃₁ N ₃ O ₃
259091	H	H	Ph	H	H	C ₂₅ H ₃₃ N ₃ O ₃
259092	H	H	H	cyclohexyl	H	C ₂₅ H ₃₉ N ₃ O ₃
259093	H	H	H	cyclopentyl	cyclopentyl-OCO-CH2O	C ₃₁ H ₄₇ N ₃ O ₆



259089: C21-H32-N2-O3



259090: C19-H33-N3-O4

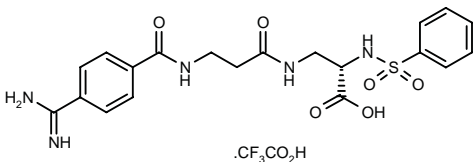
SOURCE – Boehringer Ingelheim..

REFERENCES

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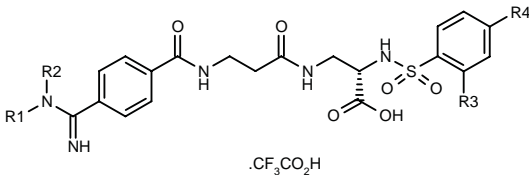
258782

3-[3-(4-Amidinobenzamido)propionamido]-2(*S*)-(phenyl-sulfonamido)propionic acid trifluoroacetate

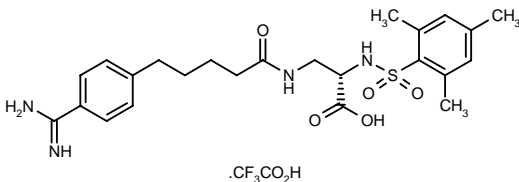


C20-H23-N5-O6-S.C2-H-F3-O2; Mol wt: 575.52

ACTION – Platelet aggregation inhibitor, a fibrinogen (gplIb/IIIa) receptor antagonist (IC₅₀ = 4.6 nM) with much lower affinity for fibronectin and vitronectin receptors (IC₅₀ = 0.2 and 1.0 μM, respectively). Compound inhibited ADP-induced platelet aggregation both *in vitro* using human platelet-rich plasma (PRP; IC₅₀ = 16 nM) and *ex vivo* in guinea pigs (100% inhibition at 6 h after administration of 0.1 mg/kg p.o.). Other compounds from this series of 2,3-diaminopropionic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
259101	H	H	CF3	H	C ₂₁ H ₂₂ F ₃ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259102	H	H	Me	H	C ₂₁ H ₂₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259103	H	H	H	Me	C ₂₁ H ₂₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259104	H	H	NO2	H	C ₂₀ H ₂₂ N ₆ O ₅ S.C ₂ HF ₃ O ₂
259105	H	H	H	F	C ₂₀ H ₂₂ FN ₅ O ₆ S.C ₂ HF ₃ O ₂
259403	H	Me	H	H	C ₂₁ H ₂₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259404	H	Et	H	H	C ₂₂ H ₂₇ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259405	Me	Me	H	H	C ₂₂ H ₂₇ N ₅ O ₆ S.C ₂ HF ₃ O ₂



259402: C24-H32-N4-O5-S.C2-H-F3-O2

SOURCE – Sumitomo.

REFERENCES

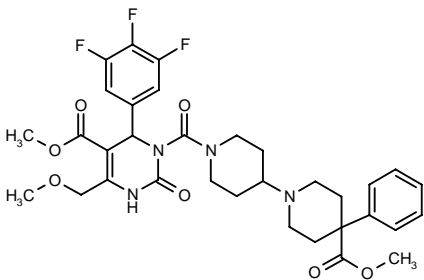
1. Ikeda, Y. et al. (Sumitomo Pharm. Co., Ltd.) *2,3-Diaminopropionic acid deriv.* US 5707994, WO 9511228.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

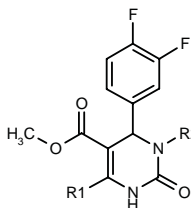
258967

3-[4-[4-(Methoxycarbonyl)-4-phenylpiperidin-1-yl]-piperidin-1-ylcarbonyl]-6-(methoxymethyl)-2-oxo-4-(3,4,5-trifluorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

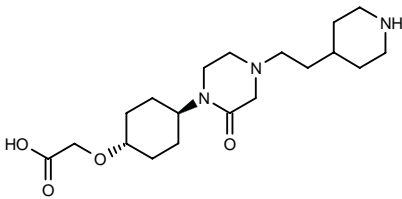


C33-H37-F3-N4-O7; Mol wt: 658.67

ACTION – Selective human α_{1A}-adrenoceptor antagonist with potential for the treatment of benign prostatic hyperplasia, impotence, pain and cardiac arrhythmia, as well as for lowering intraocular pressure and inhibiting cholesterol synthesis. Other compounds from this series of specifically claimed dihydropyrimidines include the following:



Compound	R1	R2	Formula
259505	Me	4-(2-NO2-Ph)-2(S)-Me-1-Piz-(CH2)3NHCO	C ₂₈ H ₃₂ F ₂ N ₆ O ₆
259506	CH2OMe	4-(2-MeO-5-Me-Ph)-4-Ph-1-Pip-(CH2)3NHCO	C ₃₇ H ₄₂ F ₂ N ₄ O ₆
259507	CH2OMe	4-Ph-4-(2-thienyl)-1-Pip-(CH2)3NHCO	C ₃₃ H ₃₆ F ₂ N ₄ O ₅ S
259508	Me	(S)-4-CN-4-Ph-1-Pip-CH2CH(Me)(CH2)3	C ₃₁ H ₃₆ F ₂ N ₄ O ₃
259509	Me	(S)-4-[2-(CONH2)-Ph]-1-Piz-CH2CH(Me)(CH2)3	C ₃₀ H ₃₇ F ₂ N ₅ O ₄
259510	Me	4-(CO2Me)-4-Ph-1-Pip-CH2CH2NHCOCH2	C ₃₀ H ₃₄ F ₂ N ₄ O ₆



259090: C19-H33-N3-O4

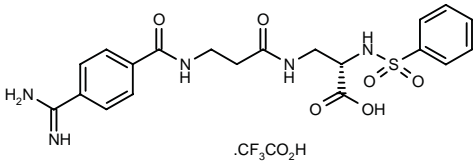
SOURCE – Boehringer Ingelheim..

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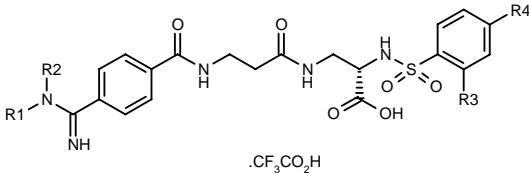
258782

3-[3-(4-Amidinobenzamido)propionamido]-2(*S*)-(phenyl-sulfonamido)propionic acid trifluoroacetate

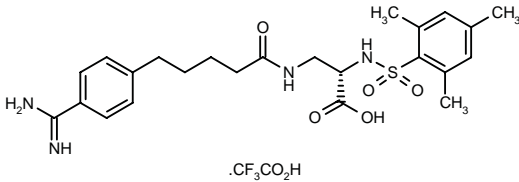


C20-H23-N5-O6-S.C2-H-F3-O2; Mol wt: 575.52

ACTION – Platelet aggregation inhibitor, a fibrinogen (gplIb/IIIa) receptor antagonist (IC₅₀ = 4.6 nM) with much lower affinity for fibronectin and vitronectin receptors (IC₅₀ = 0.2 and 1.0 μM, respectively). Compound inhibited ADP-induced platelet aggregation both *in vitro* using human platelet-rich plasma (PRP; IC₅₀ = 16 nM) and *ex vivo* in guinea pigs (100% inhibition at 6 h after administration of 0.1 mg/kg p.o.). Other compounds from this series of 2,3-diaminopropionic acid derivatives include the following:



Compound	R1	R2	R3	R4	Formula
259101	H	H	CF3	H	C ₂₁ H ₂₂ F ₃ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259102	H	H	Me	H	C ₂₁ H ₂₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259103	H	H	H	Me	C ₂₁ H ₂₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259104	H	H	NO2	H	C ₂₀ H ₂₂ N ₆ O ₅ S.C ₂ HF ₃ O ₂
259105	H	H	H	F	C ₂₀ H ₂₂ FN ₅ O ₆ S.C ₂ HF ₃ O ₂
259403	H	Me	H	H	C ₂₁ H ₂₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259404	H	Et	H	H	C ₂₂ H ₂₇ N ₅ O ₆ S.C ₂ HF ₃ O ₂
259405	Me	Me	H	H	C ₂₂ H ₂₇ N ₅ O ₆ S.C ₂ HF ₃ O ₂



259402: C24-H32-N4-O5-S.C2-H-F3-O2

SOURCE – Sumitomo.

REFERENCES

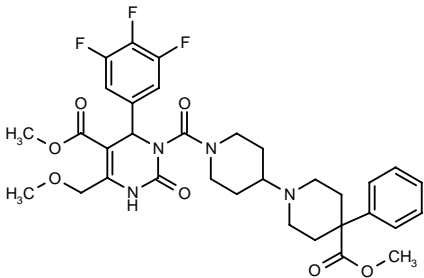
1. Ikeda, Y. et al. (Sumitomo Pharm. Co., Ltd.) *2,3-Diaminopropionic acid deriv.* US 5707994, WO 9511228.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

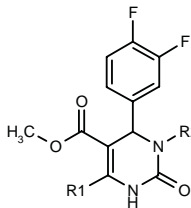
258967

3-[4-[4-(Methoxycarbonyl)-4-phenylpiperidin-1-yl]-piperidin-1-ylcarbonyl]-6-(methoxymethyl)-2-oxo-4-(3,4,5-trifluorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

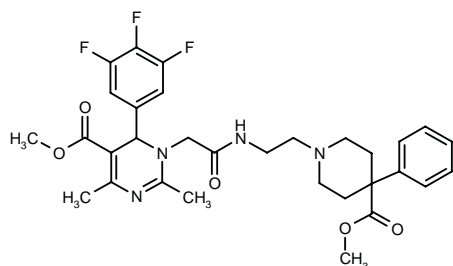


C33-H37-F3-N4-O7; Mol wt: 658.67

ACTION – Selective human α_{1A}-adrenoceptor antagonist with potential for the treatment of benign prostatic hyperplasia, impotence, pain and cardiac arrhythmia, as well as for lowering intraocular pressure and inhibiting cholesterol synthesis. Other compounds from this series of specifically claimed dihydropyrimidines include the following:



Compound	R1	R2	Formula
259505	Me	4-(2-NO2-Ph)-2(S)-Me-1-Pip-(CH2)3NHCO	C ₂₈ H ₃₂ F ₂ N ₆ O ₆
259506	CH2OMe	4-(2-MeO-5-Me-Ph)-4-Ph-1-Pip-(CH2)3NHCO	C ₃₇ H ₄₂ F ₂ N ₄ O ₆
259507	CH2OMe	4-Ph-4-(2-thienyl)-1-Pip-(CH2)3NHCO	C ₃₃ H ₃₆ F ₂ N ₄ O ₅ S
259508	Me	(S)-4-CN-4-Ph-1-Pip-CH2CH(Me)(CH2)3	C ₃₁ H ₃₆ F ₂ N ₄ O ₃
259509	Me	(S)-4-[2-(CONH2)-Ph]-1-Pip-CH2CH(Me)(CH2)3	C ₃₀ H ₃₇ F ₂ N ₅ O ₄
259510	Me	4-(CO2Me)-4-Ph-1-Pip-CH2CH2NHCOCH2	C ₃₀ H ₃₄ F ₂ N ₄ O ₆



259511: C31-H35-F3-N4-O5

SOURCE – Synaptic.

REFERENCES

1. Wong, W.C. et al. (Synaptic Pharm. Corp.) *Dihydropyrimidines and uses thereof*. WO 9742956.

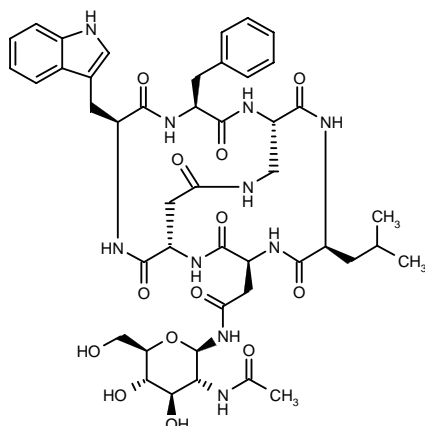
TREATMENT OF URINARY INCONTINENCE

NEPADUTANT

255471

Cyclo[*N*-[2-(acetylamino)-2-deoxy-β-D-glucopyranosyl]-L-asparaginy]-L-aspartyl-L-tryptophyl-L-phenylalanyl-[2(*S*),3-diaminopropionyl]-L-leucine]-*C*-4.2-*N*-3.5-lactam

MEN-11420



C45-H58-N10-O13; Mol wt: 947.01

ACTION – Potent, selective and competitive tachykinin NK₂ receptor antagonist with high affinity for the NK₂ receptor ($K_i = 2.5 \pm 0.7$ and 2.6 ± 0.4 nM, respectively, for displacement of [¹²⁵I]-NKA or [³H]-SR-48968 binding in CHO cells expressing human NK₂ receptors) and negligible affinity for NK₁ and NK₃ and other receptors ($pIC_{50} < 6.0$). Specificity for NK₂ receptors was also demonstrated by specific inhibition of NK₂-mediated responses in a range of both *in vitro* and *in vivo* functional assays using different species and tissues. It shows good activity after intraduodenal administration and particularly good activity after intranasal administration. Suitable for studying the pathophysiological significance of NK₂ receptors in humans and also potentially useful for the treatment of bladder hyperreflexia.

SOURCE — Menarini.

REFERENCES

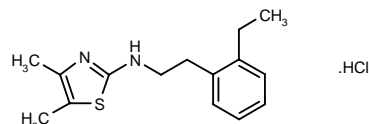
1. Arcamone, F. et al. (Menarini Ind. Farm. Riunite Srl) *Bicyclic tachykinins antagonists, preparation thereof and their use in pharmaceutical compsn*. WO 9628467.
2. Catalioto, R.M. et al. *MEN 11420 (nepadutant), a novel glycosylated bicyclic peptide tachykinin NK₂ receptor antagonist*. Brit J Pharmacol 1998, 123(1): 81.
3. Lecci, A. et al. *MEN 11,420, a peptide tachykinin NK₂ receptor antagonist, reduces motor responses induced by the intravesical administration of capsaicin in vivo*. Naunyn-Schmied Arch Pharmacol 1997, 356(2): 182.
4. Lecci, A. et al. *Role of tachykinin NK₁ and NK₂-receptors on colonic motility in anesthetized rats: Effect of agonists*. Can J Physiol Pharmacol 1997, 75(6): 582.
5. Maggi, C.A. et al. *Sequential activation of the triple excitatory transmission to the circular muscle of guinea-pig colon*. Neuroscience 1997, 79(1): 263.
6. Matsumoto, T. et al. *Effect of MEN 11420, a tachykinin NK₂ receptor antagonist, on antigen-induced airway responses in an allergic rabbit model*. Annu Cong Eur Respir Soc (Sept 20-24, Berlin) 1997, Abstr P2575.
7. Pattacchini, R. et al. *MEN 11420, a novel NK₂ receptor antagonist*. William Harvey Res Conf. Conf Tachykinins and Their Antagonists (Oct 10-11, London) 1996, 25.
8. Santicoli, P. et al. *MEN 11420, a potent and selective tachykinin NK₂ receptor antagonist in the guinea-pig and human colon*. Naunyn-Schmied Arch Pharmacol 1997, 356(5): 678.
9. Tramontana, M. et al. *Effect of MEN 11420 on tachykinin-induced bronchoconstriction in anaesthetized guinea-pigs*. Brit J Pharmacol 1997, 122(Suppl.): Abstr 417P.
10. Zagorodnyuk, V. and Maggi, C.A. *Tachykinin NK₁ and NK₂ receptors mediate non-adrenergic non-cholinergic excitatory neuromuscular transmission in the guinea-pig stomach*. Neuroscience 1997, 80(2): 625.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

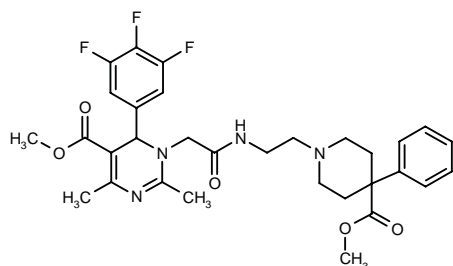
256443

N-(4,5-Dimethylthiazol-2-yl)-*N*-[2-(2-ethylphenyl)ethyl]-amine hydrochloride



C15-H20-N2-S.HCl; Mol wt: 296.86

ACTION – Gastric acid antisecretory and antiulcer agent with good inhibitory activity against *Helicobacter pylori* (MIC = 2 µg/ml), as well as good H⁺/K⁺-ATPase-inhibitory activity (IC₅₀ = 0.017 µM). Other representative compounds within this series of 2-aminothiazole derivatives include the following:



259511: C31-H35-F3-N4-O5

SOURCE – Synaptic.

REFERENCES

1. Wong, W.C. et al. (Synaptic Pharm. Corp.) *Dihydropyrimidines and uses thereof*. WO 9742956.

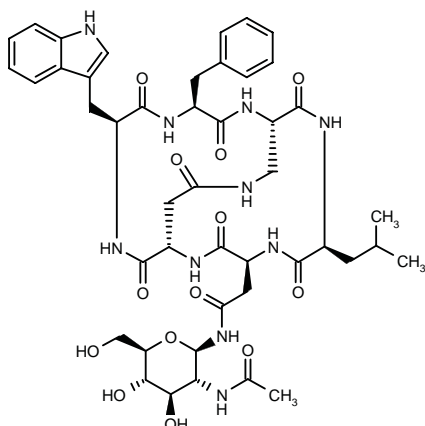
TREATMENT OF URINARY INCONTINENCE

NEPADUTANT

255471

Cyclo[*N*-[2-(acetylamino)-2-deoxy-β-D-glucopyranosyl]-L-asparaginy]-L-aspartyl-L-tryptophyl-L-phenylalanyl-[2(*S*),3-diaminopropionyl]-L-leucine]-*C*-4.2-*N*-3.5-lactam

MEN-11420



C45-H58-N10-O13; Mol wt: 947.01

ACTION – Potent, selective and competitive tachykinin NK₂ receptor antagonist with high affinity for the NK₂ receptor ($K_i = 2.5 \pm 0.7$ and 2.6 ± 0.4 nM, respectively, for displacement of [¹²⁵I]-NKA or [³H]-SR-48968 binding in CHO cells expressing human NK₂ receptors) and negligible affinity for NK₁ and NK₃ and other receptors ($pIC_{50} < 6.0$). Specificity for NK₂ receptors was also demonstrated by specific inhibition of NK₂-mediated responses in a range of both *in vitro* and *in vivo* functional assays using different species and tissues. It shows good activity after intraduodenal administration and particularly good activity after intranasal administration. Suitable for studying the pathophysiological significance of NK₂ receptors in humans and also potentially useful for the treatment of bladder hyperreflexia.

SOURCE — Menarini.

REFERENCES

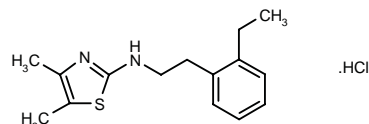
1. Arcamone, F. et al. (Menarini Ind. Farm. Riunite Srl) *Bicyclic tachykinins antagonists, preparation thereof and their use in pharmaceutical compsn*. WO 9628467.
2. Catalioto, R.M. et al. *MEN 11420 (nepadutant), a novel glycosylated bicyclic peptide tachykinin NK₂ receptor antagonist*. Brit J Pharmacol 1998, 123(1): 81.
3. Lecci, A. et al. *MEN 11,420, a peptide tachykinin NK₂ receptor antagonist, reduces motor responses induced by the intravesical administration of capsaicin in vivo*. Naunyn-Schmied Arch Pharmacol 1997, 356(2): 182.
4. Lecci, A. et al. *Role of tachykinin NK₁ and NK₂-receptors on colonic motility in anesthetized rats: Effect of agonists*. Can J Physiol Pharmacol 1997, 75(6): 582.
5. Maggi, C.A. et al. *Sequential activation of the triple excitatory transmission to the circular muscle of guinea-pig colon*. Neuroscience 1997, 79(1): 263.
6. Matsumoto, T. et al. *Effect of MEN 11420, a tachykinin NK₂ receptor antagonist, on antigen-induced airway responses in an allergic rabbit model*. Annu Cong Eur Respir Soc (Sept 20-24, Berlin) 1997, Abst P2575.
7. Pattacchini, R. et al. *MEN 11420, a novel NK₂ receptor antagonist*. William Harvey Res Conf. Conf Tachykinins and Their Antagonists (Oct 10-11, London) 1996, 25.
8. Santicoli, P. et al. *MEN 11420, a potent and selective tachykinin NK₂ receptor antagonist in the guinea-pig and human colon*. Naunyn-Schmied Arch Pharmacol 1997, 356(5): 678.
9. Tramontana, M. et al. *Effect of MEN 11420 on tachykinin-induced bronchoconstriction in anaesthetized guinea-pigs*. Brit J Pharmacol 1997, 122(Suppl.): Abst 417P.
10. Zagorodnyuk, V. and Maggi, C.A. *Tachykinin NK₁ and NK₂ receptors mediate non-adrenergic non-cholinergic excitatory neuromuscular transmission in the guinea-pig stomach*. Neuroscience 1997, 80(2): 625.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

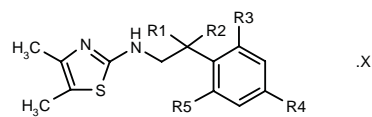
256443

N-(4,5-Dimethylthiazol-2-yl)-*N*-[2-(2-ethylphenyl)ethyl]-amine hydrochloride



C15-H20-N2-S.HCl; Mol wt: 296.86

ACTION – Gastric acid antisecretory and antiulcer agent with good inhibitory activity against *Helicobacter pylori* (MIC = 2 µg/ml), as well as good H⁺/K⁺-ATPase-inhibitory activity (IC₅₀ = 0.017 µM). Other representative compounds within this series of 2-aminothiazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
260409	H	H	Me	H	Me	HCl	C ₁₅ H ₂₀ N ₂ S.HCl
260410	H	OH	Me	F	H	HCl	C ₁₄ H ₁₇ FN ₂ OS.HCl
260411	H	Me	H	F	H	HCl	C ₁₄ H ₁₇ N ₂ S.HCl
260413	H	Me	H	H	H		C ₁₄ H ₁₈ N ₂ S
260414	H	CONHCH2Ph	Me	H	H	HCl	C ₂₂ H ₂₅ N ₃ OS.HCl
260415		-CH2-	Me	H	Me	HCl	C ₁₆ H ₂₀ N ₂ S.HCl
260416	H	Me	Cl	H	Cl	HCl	C ₁₄ H ₁₆ Cl ₂ N ₂ S.HCl

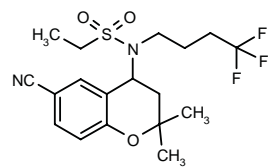
SOURCE – Toyama.

REFERENCES

1. Shibata, H. et al. (Toyama Chem. Co., Ltd.) 2-Aminothiazole derivs. or the salts thereof. JP 97235278.

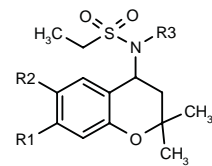
258594

N-(6-Cyano-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-yl)-N-(4,4,4-trifluorobutyl)ethanesulfonamide



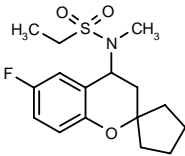
C18-H23-F3-N2-O3-S; Mol wt: 404.45

ACTION – Gastric antisecretory agent that blocks cAMP-dependent K⁺ channels (IC₅₀ = 0.42 μM). Antisecretory activity was evaluated by measuring inhibition of aminopyrine accumulation in rabbit gastric glands stimulated by histamine or carbachol. Also claimed for use as an antiarrhythmic agent. Other specifically claimed sulfonamide-substituted chromanes include the following:



Compound	R1	R2	R3	Formula
259808	H	F	Me	C ₁₄ H ₂₀ FN ₂ O ₃ S
260795	H	CN	Me	C ₁₅ H ₂₀ N ₂ O ₃ S
260796	H	CO2Me	Me	C ₁₆ H ₂₃ NO ₅ S
260797	H	CN	Bu	C ₁₈ H ₂₆ N ₂ O ₃ S
260798	H	Me	Me	C ₁₅ H ₂₃ NO ₃ S
260799	Cl	F	Me	C ₁₄ H ₁₉ ClFNO ₃ S
260800	Cl	Cl	Me	C ₁₄ H ₁₉ Cl ₂ NO ₃ S
260801	H	F	Bu	C ₁₇ H ₂₆ FN ₂ O ₃ S
260803	H	F	(CH2)3CF3	C ₁₇ H ₂₃ F ₄ NO ₃ S
260804	H	F	C6H13	C ₁₉ H ₃₀ FN ₂ O ₃ S
260805	H	Et	(CH2)3CF3	C ₁₉ H ₂₈ F ₃ NO ₃ S
260806	H	F	CH2CO2Et	C ₁₇ H ₂₄ FN ₂ O ₅ S

Compound	R1	R2	R3	Formula
260807	H	O(CH2)3CF3	Me	C ₁₈ H ₂₅ F ₃ NO ₄ S
260808	H	4-Br-Ph	Me	C ₂₀ H ₂₄ BrNO ₃ S
260809	H	Me	(CH2)3OEt	C ₁₉ H ₃₁ NO ₄ S



260802: C16-H22-F-N-O3-S

SOURCE – Hoechst Marion Roussel.

REFERENCES

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DA-9601

250870

Quality-controlled extract of dried aerial parts of *Artemisia asiatica*

ACTION – Mucoprotective agent extracted from *Artemisia asiatica*, proven to exert gastroprotective effects in arthritic rats treated chronically with the nonsteroidal antiinflammatory drug (NSAID) naproxen (47.8, 73.2 and 67.9% inhibition of gastric lesions at doses of 50, 100 and 200 mg/kg p.o., respectively) without influencing the antiinflammatory/analgesic effects of the drug. The compound also provided dose-dependent protection against experimental colitis induced by trinitrobenzene sulfonic acid (TNB) in a rat model of inflammatory bowel disease, doses of 5-125 mg/kg/day in the diet being more effective than mesalazine 25-50 mg/kg/day. DA-9601 is currently undergoing clinical trials for the treatment of acute and chronic gastritis in Korea.

SOURCE – Dong-A.

REFERENCES

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2. Kim, O.-J. et al. Four-week oral toxicity study of DA-9601, an antiulcer agent of *Artemisia* spp. extract in rats. J Appl Pharmacol 1996, 4: 354.

3. Lee, E.B. et al. General pharmacology of *Artemisia* extract powder, DA-9601. J Appl Pharmacol 1996, 4: 174.

4. Oh, T.Y. et al. Studies on antiulcer effects of DA-9601, an *Artemisiae Herba* extract against experimental gastric ulcers and its mechanism. J Appl Pharmacol 1996, 4: 111.

5. Oh, T.Y. et al. Studies on protective effect of DA-9601, an *Artemisiae Herba* extract, against ethanol-induced gastric mucosal damage and its mechanism. J Appl Pharmacol 1997, 5: 202.

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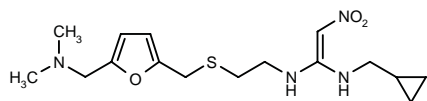
7. Oh, T.Y. et al. Protective effect of DA-9601, an extract of *Artemisiae herba*, against naproxen-induced gastric damage in arthritic rats. Arch Pharm Res 1997, 20(5): 414.

8. Oh, T.Y. et al. Beneficial effects of DA-9601, extract of *Artemisia asiatica*, in TNB-induced experimental colitis in the rat. Gastroenterology 1997, 112(4, Suppl.): A1054.

JB-9315

259977

(*E*)-*N*-(Cyclopropylmethyl)-*N'*-[2-[5-(dimethylamino-methyl)-furan-2-ylmethylsulfanyl]ethyl]-2-nitrovinylene-1,1-diamine



C16-H26-N4-O3-S; Mol wt: 354.47

ACTION – Antiulcer agent, a derivative of ranitidine that acts as a specific, competitive histamine H₂ receptor antagonist (pA₂ = 7.30 for inhibition of the chronotropic effects of histamine on isolated guinea pig right atria); it has no significant effect against histamine- or acetylcholine-induced contractions in guinea pig ileum and rat duodenum, respectively, thus demonstrating selectivity for H₂ receptors. Antisecretory effects were demonstrated against histamine-, pentagastrin- and carbachol-stimulated gastric acid secretion in lumen-perfused rats (ID₅₀ = 5.85, 4.35 and 4.08 mg/kg i.v., respectively, at 1-2 h). It also dose-dependently (30-100 mg/kg i.p.) reduced gastric acid secretion (ID₅₀ = 32.85 mg/kg i.p.), gastric juice volume and pepsin secretion in pylorus-ligated rats. JB-9315 was able to prevent the gastric lesions induced by cold stress plus indomethacin in rats (ID₅₀ = 6.85 mg/kg p.o.) and decrease the formation of absolute ethanol-induced gastric hemorrhagic lesions (71.6% at a dose of 100 mg/kg p.o.). Although it was less active than ranitidine in most of these assays, unlike ranitidine, it increased gastric mucus production, indicating gastroprotective properties in addition to its antiulcer and antisecretory effects.

SOURCE – Univ. Salamanca, Salamanca (ES).

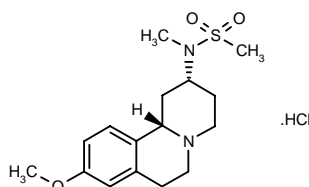
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2. Palacios, B. et al. *Pharmacology of JB-9315, a new selective histamine H₂-receptor antagonist*. *Gen Pharmacol* 1998, 30(2): 181.

IRRITABLE BOWEL SYNDROME THERAPY

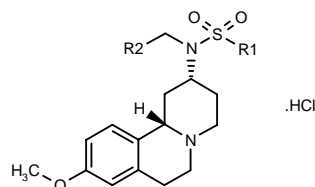
257735

(2*R*,11*bS*)-*N*-(9-Methoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-benzo[*a*]quinolizin-2-yl)-*N*-methylmethanesulfonamide hydrochloride



C16-H24-N2-O3-S.HCl; Mol wt: 360.90

ACTION – Agent for the treatment of irritable bowel syndrome (IBS) with high efficacy in two rat models of IBS after s.c. or oral administration. No mortality was observed following administration of 250 mg/kg p.o. to mice. Other compounds from this series of benzoquinolizine derivatives include the following:



Compound	R1	R2	Isomer	Formula
259969	Me	H	2 <i>R</i> ⁺ ,11 <i>bS</i> ⁺	C ₁₆ H ₂₄ N ₂ O ₃ S.HCl
259970	4-MeO-Ph	H	2 <i>R</i> ⁺ ,11 <i>bS</i> ⁺	C ₂₂ H ₂₈ N ₂ O ₄ S.HCl
259971	Ph	H	2 <i>R</i> ⁺ ,11 <i>bS</i> ⁺	C ₂₁ H ₂₆ N ₂ O ₃ S.HCl
259972	4-F-Ph	H	2 <i>R</i> ⁺ ,11 <i>bS</i> ⁺	C ₂₁ H ₂₆ N ₂ O ₃ S.HCl
259973	2,5-(MeO)2-Ph	H	2 <i>R</i> ⁺ ,11 <i>bS</i> ⁺	C ₂₃ H ₃₀ N ₂ O ₅ S.HCl
259974	N(Me)2	H	2 <i>R</i> ⁺ ,11 <i>bS</i> ⁺	C ₁₇ H ₂₇ N ₃ O ₃ S.HCl
259975	Et	H	2 <i>R</i> ,11 <i>bS</i>	C ₁₇ H ₂₆ N ₂ O ₃ S.HCl
259976	Me	Me	2 <i>R</i> ,11 <i>bS</i>	C ₁₇ H ₂₈ N ₂ O ₃ S.HCl

SOURCE – Nippon Shinyaku.

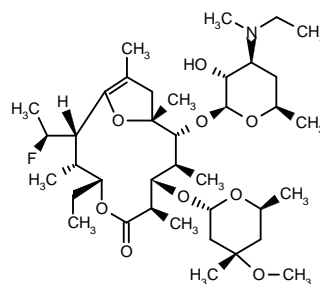
REFERENCES

1. Yamamoto, O. and Shirouchi, Y. (Nippon Shinyaku Co., Ltd.) *Benzoquinolizine derivs. and medicinal compsns.* WO 9740046.

ANTIDIARRHEAL AGENTS

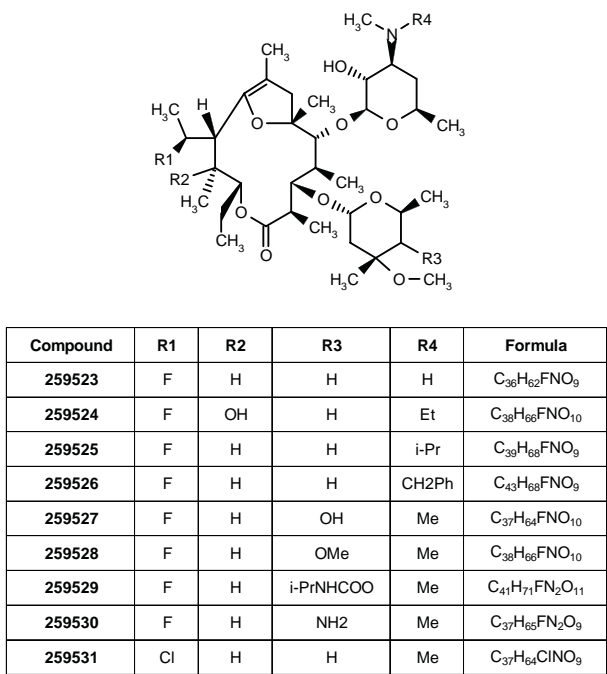
259390

[2*R*-(2α,3α,4α,5β,6β,10β,11β,12α)]-6,9-Epoxy-10-[1(*S*)-fluoroethyl]-3-[4(*S*)-methoxy-4,6(*S*)-dimethyltetrahydropyran-2(*S*)-yloxy]-2,4,6,8,11-pentamethyl-5-[3,4,6-trideoxy-3-(*N*-ethyl-*N*-methylamino)-β-D-glucopyranosyloxy]-8-tetradeceno-12-lactone



C38-H66-F-N-O9; Mol wt: 699.94

ACTION – Motilin antagonist for the treatment of gastrointestinal disorders, especially those associated with hypermotility such as diarrhea, irritable bowel syndrome, Crohn's disease and ulcerative colitis, and obesity. Compound exhibited strong motilin binding with a pK_d of 7.94 against [¹²⁵I]-motilin binding to receptors isolated from rabbit antral smooth muscle (pK_d motilin = 9.1), but did not induce contractions in rabbit duodenal smooth muscle. It has negligible antibacterial potency as compared to parent erythromycin antibiotics. Other exemplified macrocyclic 13-membered-ring derivatives of erythromycins A and B include the following:



SOURCE – Abbott.

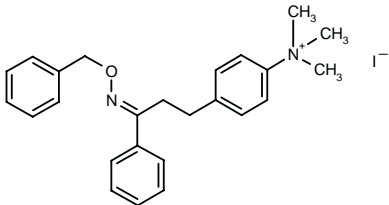
REFERENCES

1. Lartey, P.A. et al. (Abbott Labs.) *Macrocyclic 13-membered ring derivs. of erythromycin A and B*. US 5712253, WO 9748713.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

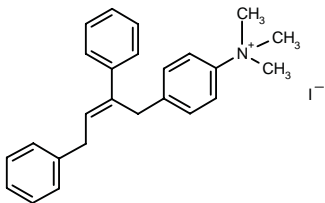
256481

(E)-4-[3-(Benzyloxyimino)-3-phenylpropyl]-N,N,N-trimethylanilinium iodide

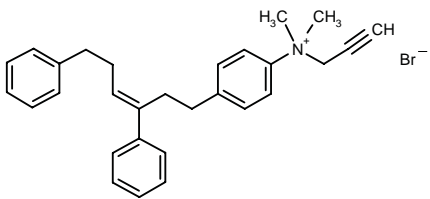


C25-H29-I-N2-O; Mol wt: 500.42

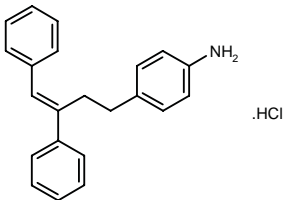
ACTION – Gastrointestinal prokinetic agent with affinity for motilin receptors, proven to stimulate acetylcholine-induced contractions in isolated rabbit duodenal longitudinal muscle strips. A representative compound from a series of allylalkane derivatives, wherein the following are also included:



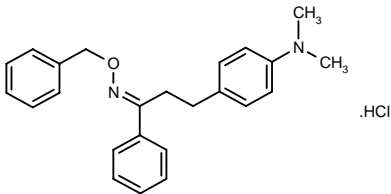
260405: C25-H28-I-N



260406: C29-H32-Br-N



260407: C22-H21-N.HCl



260408: C24-H26-N2-O.HCl

SOURCE – Taisho.

REFERENCES

1. Suzuki, M. and Ouchi, Y. (Taisho Pharm. Co., Ltd.) *Allylalkane derivs.* JP 97249620.

258596

N-Methyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-glutamyl-alanyl-arginyl-leucyl-lysyl-lysineamide C-5.10-N-6.14-amide

C87-H133-N21-O20; Mol wt: 1793.14

ACTION – Cyclic motilin-like polypeptide with potent gastrointestinal motility-stimulating activity and enhanced metabolic stability. Its motilin receptor binding affinity was evaluated *in vitro* in rabbit antral smooth muscle membranes using porcine [¹²⁵I-Tyr⁷,Nle¹³]-motilin as the radioligand (pIC₅₀ = 9.20). In addition, it exhibited potent activity when assessed for its ability to constrict rabbit duodenal smooth muscle (pEC₅₀ = 7.96) and canine gastrointestinal tract (ED₅₀ = 0.002 nM). Other specifically claimed motilin-like cyclopeptides include the following:

N-Methyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-aspartyl-alanyl-arginyl-leucyl-lysineamide C-4.10-N-6.14-amide

259406; C80-H119-N19-O19

N-Methyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-glutamyl-glutaminyl-arginyl-leucyl-lysineamide C-5.10-N-6.14-amide

259407; C83-H124-N20-O20

N,N,N-Trimethyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-aspartyl-alanyl-arginyl-leucyl-lysyl-D-lysineamide C-4.10-N-6.14-amide

259408; C88-H136-N21-O20

***N,N,N*-Trimethyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-aspartyl-alanyl-arginyl-leucyl-lysyl-lysineamide C-4.10-N-6.14-amide**

259409; C88-H136-N21-O20

***N,N,N*-Trimethyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-glutamyl-alanyl-arginyl-leucyl-lysyl-lysineamide C-5.10-N-6.14-amide**

259410; C89-H138-N21-O20

SOURCE – Ohmeda.

REFERENCES

1. Dharanipragada, R. et al. (Ohmeda Pharm. Prod. Div. Inc.) *Cyclic motilin-like polypeptides with gastrointestinal motor stimulating activity*. EP 807639, JP 98053599.

***N,N,N*-Trimethyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-aspartyl-alanyl-arginyl-leucyl-lysyl-lysineamide C-4.10-N-6.14-amide**

259409; C88-H136-N21-O20

***N,N,N*-Trimethyl-phenylalanyl-valyl-prolyl-isoleucyl-phenylalanyl-threonyl-tyrosyl-glycyl-glutamyl-glutamyl-alanyl-arginyl-leucyl-lysyl-lysineamide C-5.10-N-6.14-amide**

259410; C89-H138-N21-O20

SOURCE – Ohmeda.

REFERENCES

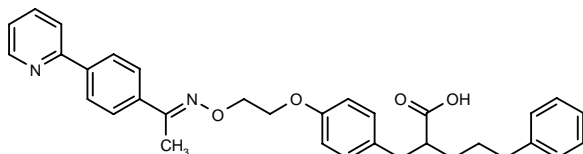
1. Dharanipragada, R. et al. (Ohmeda Pharm. Prod. Div. Inc.) *Cyclic motilin-like polypeptides with gastrointestinal motor stimulating activity*. EP 807639, JP 98053599.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

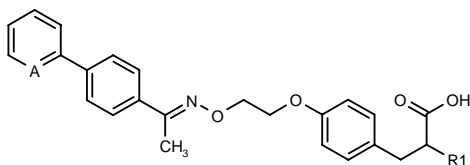
257204

5-Phenyl-2-[4-[2-[1-[4-(2-pyridyl)phenyl]ethylidene-aminoxy]ethoxy]benzyl]pentanoic acid



C33-H34-N2-O4; Mol wt: 522.64

ACTION – Hypoglycemic agent shown to decrease blood glucose levels by 47.0% in KK mice at 10 mg/kg/day x 3 days administered with food. Other compounds from this series of phenylalkylcarboxylic acid derivatives include the following:



Compound	R1	A	Formula
260049	OEt	N	C ₂₆ H ₂₈ N ₂ O ₅
260050	SPh	N	C ₃₀ H ₂₈ N ₂ O ₄ S
260051	NHPh	CH	C ₃₁ H ₃₀ N ₂ O ₄
260052	NHEt	N	C ₂₆ H ₂₈ N ₃ O ₄
260053	SMe	N	C ₂₅ H ₂₆ N ₂ O ₄ S

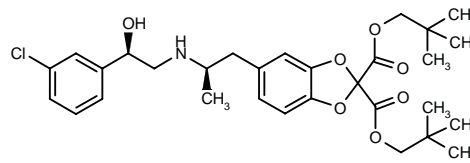
SOURCE – Sankyo.

REFERENCES

1. Yanagisawa, H. et al. (Sankyo Co., Ltd.) *Phenylalkylcarboxylic acid derivs*. JP 97323967, WO 9737970.

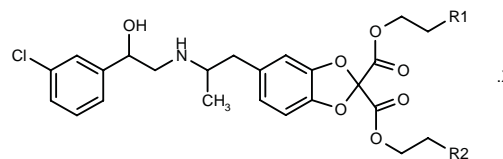
258989

5-[2(*R*)-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethylamino]-propyl]-1,3-benzodioxole-2,2-dicarboxylic acid bis(2,2-dimethylpropyl) ester



C30-H40-Cl-N-O7; Mol wt: 562.10

ACTION – Selective β_3 -adrenoceptor agonist with antidiabetic, antihyperglycemic and antiobesity properties. Agonist activity at β_3 -adrenoceptors was determined by measuring its ability to increase plasma free fatty acids in rats (ED₅₀ = 0.027 mg/kg p.o.); using human β_1 - and β_2 -adrenoceptors transfected in CHO cells, the compound gave EC₅₀ values for increase in cAMP of 5.0 and 0.325 μ M, respectively. Blood glucose-lowering activity was evaluated in db/db mice, giving an ED₅₀ of 0.028 mg/kg p.o. once daily for 3 days. Within this series of specifically claimed substituted 1,3-benzodioxoles, the following are also included:



Compound	R1=R2	X	Isomer	Formula
259736	Ph	HCl		C ₃₆ H ₃₆ ClNO ₇ ·HCl
259737	t-Bu			C ₃₂ H ₄₄ ClNO ₇
259738	i-Pr		R,R	C ₃₀ H ₄₀ ClNO ₇

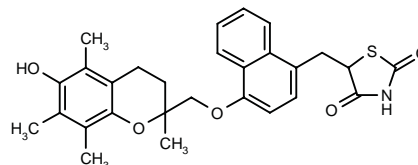
SOURCE – American Home Products.

REFERENCES

1. Gilbert, A.M. et al. (American Home Prods. Corp.) *Subst. 1,3-benzodioxoles*. WO 9743273.

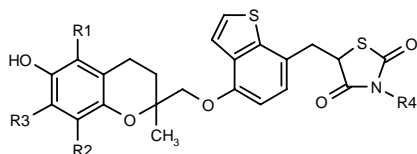
258997

5-[4-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethoxy)naphthalen-1-ylmethyl]thiazolidine-2,4-dione

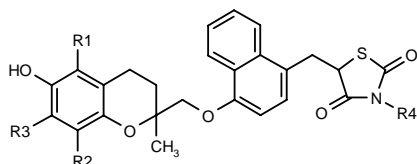


C28-H29-N-O5-S; Mol wt: 491.60

ACTION – Antidiabetic agent found to produce a 95% decrease in blood glucose levels in diabetic ob/ob mice at a dose of 100 mg/kg p.o. Other specifically claimed thiazolidinediones include the following:



Compound	R1=R2	R3	R4	Formula
259727	Me	Me	H	C ₂₆ H ₂₇ NO ₅ S ₂
259729	H	t-Bu	H	C ₂₇ H ₂₉ NO ₅ S ₂
259730	H	Me	H	C ₂₄ H ₂₃ NO ₅ S ₂
259734	Me	Me	CH ₂ OH	C ₂₇ H ₂₉ NO ₆ S ₂



Compound	R1=R2	R3	R4	Formula
259728	H	t-Bu	H	C ₂₉ H ₃₁ NO ₅ S
259731	H	Me	H	C ₂₆ H ₂₅ NO ₅ S
259732	Me	Me	CH ₂ OH	C ₂₉ H ₃₁ NO ₆ S
259735	Me	Me	t-BuCOOCH ₂	C ₃₄ H ₃₉ NO ₇ S

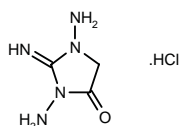
SOURCE – Boehringer Mannheim.

REFERENCES

1. Wolff, H.-P. et al. (Boehringer Mannheim GmbH) *New thiazolidinediones, process for preparing the same and medicaments containing the same.* WO 9743284.

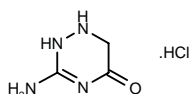
259043

1,3-Diamino-2-iminoimidazolidin-4-one hydrochloride

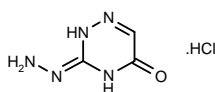


C₃-H₇-N₅-O.HCl; Mol wt: 165.58

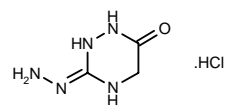
ACTION – Agent for the treatment of non-insulin-dependent diabetes mellitus whose ability to reduce blood glucose and body weight was evaluated in KKA^y mice: blood glucose T/C = 0.40 and 8.10% decrease in body weight when given for 3 days mixed with the chow at a concentration of 0.10%. Other representative compounds within this series of aminoguanidine carboxylate lactams include the following:



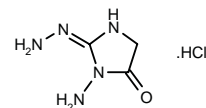
260213: C₃-H₆-N₄-O.HCl



260214: C₃-H₅-N₅-O.HCl



260216: C₃-H₇-N₅-O.HCl



260217: C₃-H₇-N₅-O.HCl

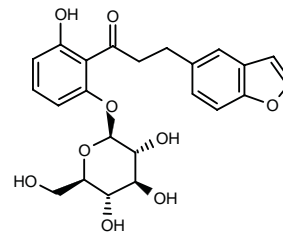
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Larsen, S.D. et al. (Pharmacia & Upjohn Co.) *Aminoguanidine carboxylate lactams for the treatment of non-insulin-dependent diabetes mellitus.* WO 9744324.

259715

3-(5-Benzofuranyl)-1-[2-(β-D-glucopyranosyloxy)-6-hydroxyphenyl]-1-propanone



C₂₃-H₂₄-O₉; Mol wt: 444.44

M.p. 73 °C.

ACTION – Antidiabetic agent, a potent Na⁺-glucose cotransporter (SGLT) inhibitor. The compound strongly increased urinary glucose levels (334 ± 32 and 591 ± 105 mg/24 h, respectively, after a single or two doses of 100 mg/kg p.o.) in rats, and it also exhibited a potent inhibitory effect on SGLT activity in rat kidney (7.9% of control using rat renal brush border membrane vesicles). Selected as a new lead for further investigation.

SOURCE – Tanabe Seiyaku.

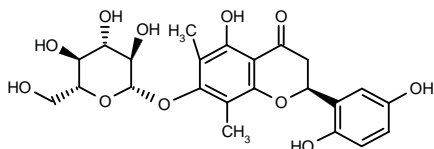
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1. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Medical compsn.* JP 97188625.
2. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Propiophenone deriv. and a process for preparing the same.* CA 2149160, EP 684254, JP 96027007, JP 96193093.
3. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Propiophenone derivs. and their preparation.* JP 97124684.
4. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Propiophenone derivs. and their preparation.* JP 97124685.
5. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Propiophenone derivs. and their preparation.* EP 773226, JP 97124686.
6. Hongu, M. et al. *Na⁺-Glucose cotransporter inhibitors as antidiabetic agents. II. Synthesis and structure-activity relationships of 4'-dehydroxyphlorizin derivatives.* Chem Pharm Bull 1998, 46(1): 22.

MYRCIACITRIN I

259717

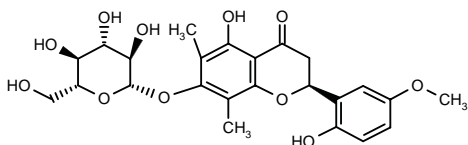
2(*S*)-2-(2,5-Dihydroxyphenyl)-7-(β-D-glucopyranosyloxy)-5-hydroxy-6,8-dimethyl-3,4-dihydro-2*H*-benzopyran-4-one



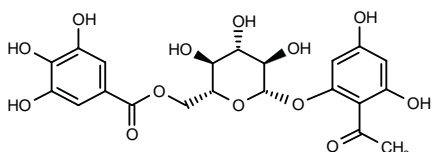
C23-H26-O11; Mol wt: 478.45

Yellow powder, $[\alpha]_D^{27} -51.0^\circ$.

ACTION – Antidiabetic flavanone glucoside isolated from the leaves of *Myrcia multiflora*, a Brazilian natural medicine used as a specific remedy for diabetes. It shows aldose reductase- and α -glucosidase-inhibitory activity ($IC_{50} = 3.2 \mu M$ for rat lens aldose reductase; $IC_{50} = 600-700 \mu M$ for rat small intestinal α -glucosidase). Other components of this natural medicine are:



Myricitrin II [259718]: C24-H28-O11



Myricaphenone B [259719]: C21-H22-O13

SOURCE – Kyoto Pharm. Univ., Kyoto (JP).

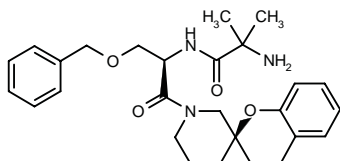
REFERENCES

1. Yoshikawa, M. et al. Antidiabetic principles of natural medicines. II. Aldose reductase and alpha-glucosidase inhibitors from Brazilian natural medicine, the leaves of *Myrcia multiflora* DC. (Myrtaceae): Structures of myricitrins I and II and myricaphenones A and B. Chem Pharm Bull 1998, 46(1): 113.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

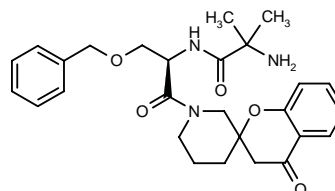
258865

(1*R*,3'*S*)-2-Amino-*N*-[1-(benzyloxymethyl)-2-(3,4-dihydrospiro[2*H*-1-benzopyran-2,3'-piperidin-1'-yl]-2-oxoethyl)-2-methylpropanamide



C27-H35-N3-O4; Mol wt: 465.59

ACTION – Potent growth hormone (GH) secretagogue that exerts its stimulatory effects through a different mechanism than endogenous GH-releasing hormone (GHRH). The agent has good oral bioavailability and was shown to induce GH release both *in vitro* ($EC_{50} = 3 \text{ nM}$ in rat pituitary cell assays) and *in vivo*, with at least a 4-fold increase in serum GH levels in dogs at doses of 0.05 mg/kg i.v. and 0.25 mg/kg p.o. Another 3-spiropiperidine-based compound is:



258864: C27-H33-N3-O5

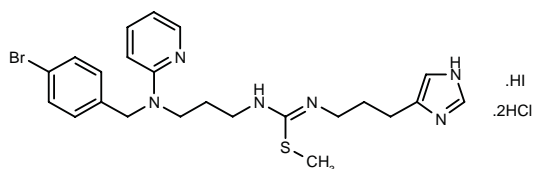
SOURCE – Merck & Co.

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1. Baldwin, J.J. et al. (Merck & Co., Inc.) Nitrogen-containing spirocycles. AU 9167873, EP 431943, JP 92217960, US 5206240.
2. Yang, L. et al. (Merck & Co., Inc.) 3-Spirolactam, 3-spiroamino, 3-spirolactone and 3-spirobenzopyran piperidines and pyrrolidines promote release of growth hormone. WO 9711697.
3. Yang, L. et al. Potent 3-spiropiperidine growth hormone secretagogues. Bioorg Med Chem Lett 1998, 8(1): 107.

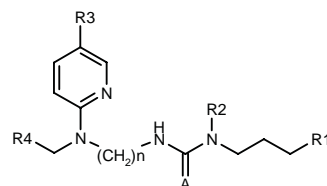
258992

1-[3-[*N*-(4-Bromobenzyl)-*N*-(2-pyridyl)amino]propyl]-3-[3-(1*H*-imidazol-4-yl)propyl]-*S*-methylisothiourea hydroiodide dihydrochloride



C23-H29-Br-N6-S.2HCl.HI; Mol wt: 702.32

ACTION – Selective, nonpeptide somatostatin receptor ligand with potential in the treatment of disorders associated with excess growth hormone secretion, diabetes, gastrointestinal disorders, malignant cell proliferative disorders and angiogenesis, and in the prevention or treatment of restenosis and vascular occlusion following vascular injury. Other compounds from this series of nonpeptide somatostatin agonists and antagonists include the following:



Compound	R1	R2	R3	R4	A	n	Formula
259487	4-imidazolyl	H	Br	3,4-(Cl)2-Ph	S	3	C ₂₂ H ₂₅ BrCl ₂ N ₆ S
259488	CH ₂ NH ₂	H	Br	3,4-(Cl)2-Ph	S	3	C ₂₀ H ₂₆ BrCl ₂ N ₅ S
259489	1-imidazolyl	H	Br	3,4-(Cl)2-Ph	S	4	C ₂₃ H ₂₇ BrCl ₂ N ₆ S
259490	4-imidazolyl	H	Br	1-Naph	S	3	C ₂₆ H ₂₉ BrN ₆ S
259492	4-imidazolyl	H	NO ₂	3,4-(Cl)2-Ph	S	2	C ₂₁ H ₂₃ Cl ₂ N ₇ O ₂ S
259493	N(Me) ₂	Me	H	4-Br-Ph	NH	3	C ₂₂ H ₃₃ BrN ₆

SOURCE – Novo Nordisk.

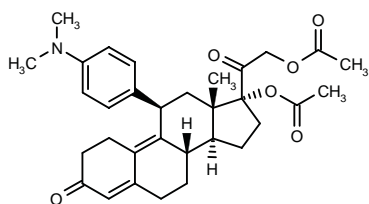
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TREATMENT OF GYNECOLOGICAL DISORDERS

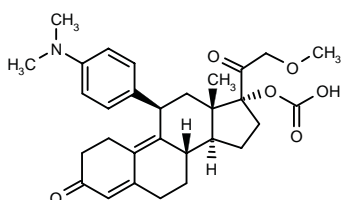
257774

17 α ,21-Diacetoxy-11 β -[4-(dimethylamino)phenyl]-19-nor-pregna-4,9-diene-3,20-dione



C32-H39-N-O6; Mol wt: 533.66

ACTION – Antiprogestational agent with reduced glucocorticoid binding affinity, claimed for use in the treatment of endometriosis, dysmenorrhea, hormone-dependent tumors and uterine fibroids, as well as for inducing menses and labor, and as a postcoital contraceptive. Another representative compound within this series of 21-substituted progesterone derivatives is:



259071: C30-H37-N-O6

SOURCE – Dept. Health Human Services, Bethesda, MD (US).

REFERENCES

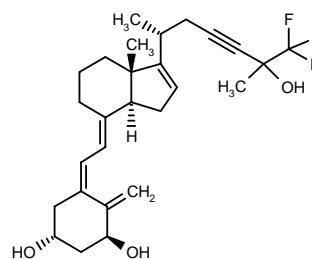
1. Kim, H.K. et al. (Dept. Health Human Services [USA]) *21-Substd. progesterone derivs. as new antiprogestational agents*. WO 9741145.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

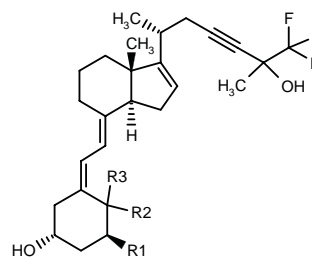
258699

26,26,26-Trifluoro-1 α ,25-dihydroxy-16,17,23,23,24,24-hexadehydrovitamin D₃



C27-H35-F3-O3; Mol wt: 464.57

ACTION – Vitamin D₃ analog for the treatment of hyperproliferative skin diseases such as psoriasis, neoplastic diseases such as leukemia and sebaceous gland diseases such as acne. *In vitro*, it was more potent than calcitriol in inducing differentiation of HL-60 cells (EC₅₀ = 0.15 nM vs. 8.0 nM for calcitriol). In addition, it potently inhibited the proliferation of human keratinocytes and human sebocytes, with IC₅₀ values of 10.0 and 1.0 nM, respectively. When evaluated for its calcemic potential in mice, it exhibited a highest tolerated dose of 1.0 μ g/kg when administered s.c. daily for 4 days. Other compounds from this series of specifically claimed fluorinated vitamin D₃ analogs include the following:



Compound	R1	R2	R3	Formula
259421	OH	H	H	C ₂₆ H ₃₅ F ₃ O ₃
259422	F	-CH2-		C ₂₇ H ₃₄ F ₄ O ₂
259423	H	-CH2-		C ₂₇ H ₃₅ F ₃ O ₂

SOURCE – Roche.

REFERENCES

1. Hennessy, B.M. and Uskokovic, M.R. (F. Hoffmann-La Roche AG) *Fluorinated vitamin D3 analogs*. EP 808831, JP 98045712.

SOURCE – Novo Nordisk.

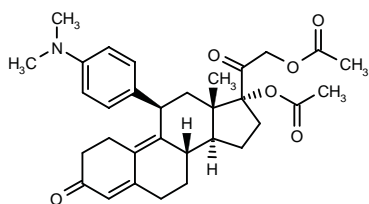
REFERENCES

1. Ankersen, M. et al. (Novo Nordisk A/S) *Somatostatin agonists and antagonists*. WO 9743278.

TREATMENT OF GYNECOLOGICAL DISORDERS

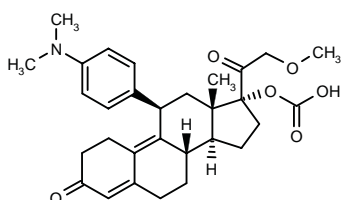
257774

17 α ,21-Diacetoxy-11 β -[4-(dimethylamino)phenyl]-19-nor-pregna-4,9-diene-3,20-dione



C32-H39-N-O6; Mol wt: 533.66

ACTION – Antiprogestational agent with reduced glucocorticoid binding affinity, claimed for use in the treatment of endometriosis, dysmenorrhea, hormone-dependent tumors and uterine fibroids, as well as for inducing menses and labor, and as a postcoital contraceptive. Another representative compound within this series of 21-substituted progesterone derivatives is:



259071: C30-H37-N-O6

SOURCE – Dept. Health Human Services, Bethesda, MD (US).

REFERENCES

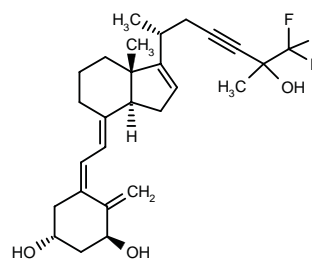
1. Kim, H.K. et al. (Dept. Health Human Services [USA]) *21-Substd. progesterone derivs. as new antiprogestational agents*. WO 9741145.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

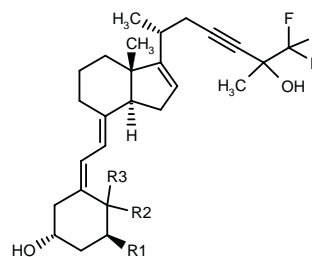
258699

26,26,26-Trifluoro-1 α ,25-dihydroxy-16,17,23,23,24,24-hexadehydrovitamin D₃



C27-H35-F3-O3; Mol wt: 464.57

ACTION – Vitamin D₃ analog for the treatment of hyperproliferative skin diseases such as psoriasis, neoplastic diseases such as leukemia and sebaceous gland diseases such as acne. *In vitro*, it was more potent than calcitriol in inducing differentiation of HL-60 cells (EC₅₀ = 0.15 nM vs. 8.0 nM for calcitriol). In addition, it potently inhibited the proliferation of human keratinocytes and human sebocytes, with IC₅₀ values of 10.0 and 1.0 nM, respectively. When evaluated for its calcemic potential in mice, it exhibited a highest tolerated dose of 1.0 μ g/kg when administered s.c. daily for 4 days. Other compounds from this series of specifically claimed fluorinated vitamin D₃ analogs include the following:



Compound	R1	R2	R3	Formula
259421	OH	H	H	C ₂₆ H ₃₅ F ₃ O ₃
259422	F	-CH2-		C ₂₇ H ₃₄ F ₄ O ₂
259423	H	-CH2-		C ₂₇ H ₃₅ F ₃ O ₂

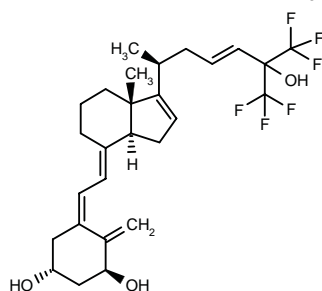
SOURCE – Roche.

REFERENCES

1. Hennessy, B.M. and Uskokovic, M.R. (F. Hoffmann-La Roche AG) *Fluorinated vitamin D3 analogs*. EP 808831, JP 98045712.

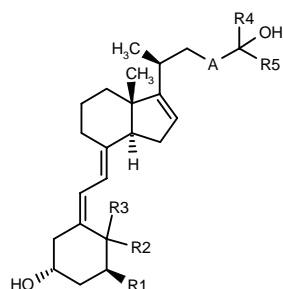
258701

(23E)-26,26,26,27,27,27-Hexafluoro-1 α ,25-dihydroxy-16,17,23,24-tetradehydro-20-epivitamin D₃



C27-H34-F6-O3; Mol wt: 520.55

ACTION – Vitamin D₃ analog for the treatment of hyperproliferative skin diseases such as psoriasis, neoplastic diseases such as leukemia or breast cancer and sebaceous gland diseases such as acne, as well as for reversing photodamage in sun-exposed skin. *In vitro*, it was more potent than 1,25-dihydroxycholecalciferol in inducing the differentiation of HL-60 cells (EC₅₀ = 0.37 nM vs. 6.0 nM for 1,25-dihydroxycholecalciferol) and in inhibiting the proliferation of breast carcinoma T47-D cells, human keratinocytes and human sebaceous cells (IC₅₀ = 10.0, 0.7 and < 10 nM, respectively, vs. 81.0, 55.0 and 50 nM, respectively, for 1,25-dihydroxycholecalciferol), while exhibiting reduced calcemic activity. Compound was also shown to reverse UVB-induced dermal damage in hairless mice following topical application. For topical or systemic administration. Other compounds from this series of specifically claimed vitamin D₃ analogs include the following:



Compound	R1	R2	R3	R4=R5	A	Formula
259470	OH	-CH2-		Me	ethynylene	C ₂₇ H ₃₈ O ₃
259471	OH	-CH2-		Me	(CH2)2	C ₂₇ H ₄₂ O ₃
259472	OH	-CH2-		CF3	ethynylene	C ₂₇ H ₃₂ F ₆ O ₃
259473	OH	-CH2-		CF3	(Z)-CH=CH	C ₂₇ H ₃₄ F ₆ O ₃
259474	OH	H	H	CF3	(Z)-CH=CH	C ₂₆ H ₃₄ F ₆ O ₃
259475	F	-CH2-		CF3	ethynylene	C ₂₇ H ₃₁ F ₇ O ₂
259476	F	-CH2-		CF3	(E)-CH=CH	C ₂₇ H ₃₃ F ₇ O ₂
259477	OH	-CH2-		Et	ethynylene	C ₂₈ H ₄₂ O ₃
259478	OH	H	H	Et	ethynylene	C ₂₈ H ₄₂ O ₃
259479	F	-CH2-		Et	ethynylene	C ₂₉ H ₄₁ FO ₂
259480	F	-CH2-		Et	(E)-CH=CH	C ₂₉ H ₄₃ FO ₂
260564	F	-CH2-		CF3	(Z)-CH=CH	C ₂₇ H ₃₃ F ₇ O ₂

SOURCE – Roche.

REFERENCES

1. Batcho, A.D. et al. (F. Hoffmann-La Roche AG) *Vitamin D₃ analogs*. EP 808833.

IR-502

257948

Combination of two peptides derived from T-cell receptors (V β 3, V β 13.1) in incomplete Freund's adjuvant (IFA)

ACTION – T-cell receptor-based vaccine for psoriasis that consists of a combination of two T-cell receptor-derived peptides (V β 3 and V β 13.1) plus an adjuvant, designed to turn off the specific immune system cells believed to cause the disease. IR-502 is undergoing phase II clinical trials.

SOURCE – Immune Response.

REFERENCES

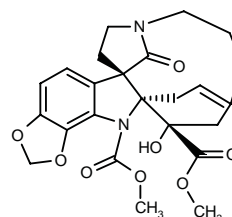
1. Brostoff, S.W. *T cell receptor peptide vaccines as immunotherapy for autoimmune disease*. IBC 3rd Annu Conf Vaccines. New Adv Technol Appl (Feb 26-27, Rockville) 1996.
2. Brostoff, S. *T cell receptor peptide vaccines as immunotherapy for psoriasis*. IBC Conf Psoriasis. Latest Adv Underst Ther Dev (Dec 4-5, Lake Buena Vista) 1995.
3. Chang, J.C. et al. *Persistence of T-cell clones in psoriatic lesions*. Arch Dermatol 1997, 133(6): 703.
4. Gottlieb, A.B. *Immunopathogenesis of psoriasis. The road from bench to bedside is a 2-way street*. Arch Dermatol 1997, 133(6): 781.
5. Morgan, E.E. *Clinical trials using T-cell receptor peptides in autoimmune diseases*. IBC Conf Autoimmune Dis. Exploiting Mech Drug Dev Diagn (Sept 29-30, San Francisco) 1997.
6. *Antipsoriatic treatment in development at Immune Response*. Prous Science Daily Essentials March 15, 1996.
7. *Phase II begins for psoriasis vaccine*. Prous Science Daily Essentials November 20, 1997.
8. *Study results reported for Immune Response antipsoriatic agent*. Prous Science Daily Essentials January 8, 1997.
9. *The Immune Response Corporation announces results from phase II clinical trials for rheumatoid arthritis and psoriasis*. The Immune Response Corp. Press Release 1997, January 7.
10. *The Immune Response Corp. reports on T-cells involved in psoriasis*. Prous Science Daily Essentials July 23, 1997.

MISCELLANEOUS DERMATOLOGIC DRUGS

PAUCIFLORINE A

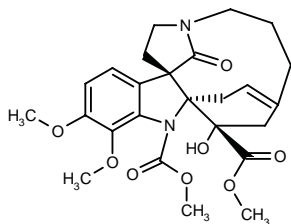
256469

(5bS,14aS,16S)-16-Hydroxy-18-oxo-7,9,10,11,14,15-hexahydro-4H-12,14a-ethano-5b-methanoazacycloundecino[5,4-b][1,3]dioxolo[4,5-g]indole-15,16-dicarboxylic acid dimethyl ester



C24-H26-N2-O8; Mol wt: 470.48

ACTION – Melanin biosynthesis inhibitor isolated from the plant *Kopsia pauciflora* HOOK, proven to inhibit melanin biosynthesis in cultured murine B16 melanoma cells at a concentration of 25 µg/ml, with no cytotoxicity. Another compound isolated from the same source is:



Pauciflorine B [260376]: C₂₅-H₃₀-N₂-O₈

SOURCE – Terumo.

REFERENCES

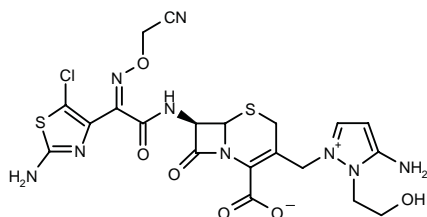
1. Takahashi, H. et al. (Terumo Corp.) *Novel cpds. and melanin biosynthesis inhibitor*. JP 97255683.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

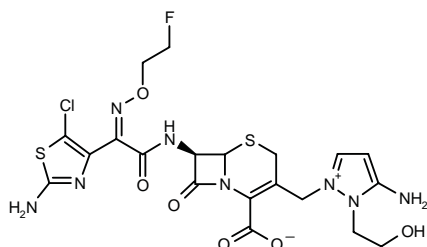
257769

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(Z)-(cyano-methoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)pyrazolium-2-ylmethyl]-3-cephem-4-carboxylate



C₂₀-H₂₀-Cl-N₉-O₆-S₂; Mol wt: 582.01

ACTION – Cephem antibiotic proven active against *Staphylococcus aureus* 3004 (MIC = 6.25 µg/ml). Another specifically claimed 3-pyrazoliomethylcephem compound is:



259133: C₂₀-H₂₂-Cl-F-N₈-O₆-S₂

SOURCE – Fujisawa.

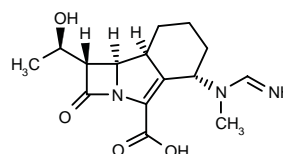
REFERENCES

1. Kawabata, K. et al. (Fujisawa Pharm. Co., Ltd.) *3-Pyrazoliomethylcephem cpds. as antimicrobial agents*. WO 9741128.

GV-129606

259302

(1S,5S,8aS,8bR)-1-[1(R)-Hydroxyethyl]-5-[N-(iminomethyl)-N-methylamino]-2-oxo-1,2,5,6,7,8,8a,8b-octahydroazeto[2,1-a]isoindole-4-carboxylic acid



C₁₅-H₂₁-N₃-O₄; Mol wt: 307.35

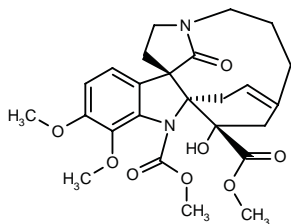
ACTION – Potent parenteral trinem antibiotic that combines broad-spectrum activity and high potency and resistance to β-lactamases. It displayed antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria, giving MIC₉₀ values of < 0.015-0.03 µg/ml against penicillin- or methicillin-susceptible staphylococci and streptococci, and 8 µg/ml against methicillin-resistant *Staphylococcus aureus* and vancomycin-susceptible *Enterococcus faecalis*; MIC₉₀ values against Gram-negative bacteria including ceftazidime-resistant isolates and *Pseudomonas aeruginosa* were 0.06-8 µg/ml, and against the anaerobic strains *Clostridium perfringens* and *Bacteroides fragilis* 0.12-0.5 µg/ml. GV-129606 exhibited *in vivo* activity against septicemia in mice caused by Gram-positive (ED₅₀ = 0.05 mg/kg s.c. or less) and Gram-negative bacteria (ED₅₀ = 0.71 mg/kg s.c. or less).

SOURCE – Glaxo Wellcome.

REFERENCES

1. Perboni, A. et al. (Glaxo SpA) *Antibacterial condensed carbapenems*. EP 502468, EP 575375, JP 94505018, US 5426104, WO 9215586, WO 9215288.
2. Di Modugno, E. et al. *In vitro and in vivo antibacterial activities of GV129606, a new broad-spectrum trinem*. Antimicrobial Agents Chemother 1997, 41(12): 2742.
3. Pecunioso, A. et al. *Synthesis and enantiomeric excess determination of (6S)-1-(trimethylsilyloxy)-6-(N-methyl-N-benzoyloxycarbonylamino)-cyclohexene*. Tetrahedron Asymmetry 1997, 8(5): 775.

ACTION – Melanin biosynthesis inhibitor isolated from the plant *Kopsia pauciflora* HOOK, proven to inhibit melanin biosynthesis in cultured murine B16 melanoma cells at a concentration of 25 µg/ml, with no cytotoxicity. Another compound isolated from the same source is:



Pauciflorine B [260376]: C₂₅-H₃₀-N₂-O₈

SOURCE – Terumo.

REFERENCES

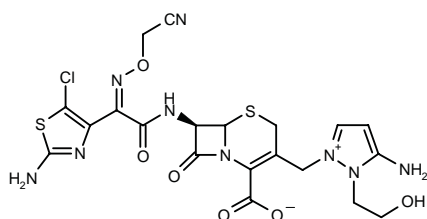
1. Takahashi, H. et al. (Terumo Corp.) *Novel cpds. and melanin biosynthesis inhibitor*. JP 97255683.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

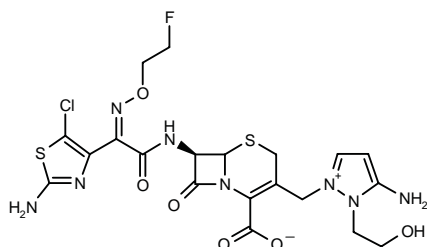
257769

7β-[2-(2-Amino-5-chlorothiazol-4-yl)-2(Z)-(cyano-methoxyimino)acetamido]-3-[5-amino-1-(2-hydroxyethyl)pyrazolium-2-ylmethyl]-3-cephem-4-carboxylate



C₂₀-H₂₀-Cl-N₉-O₆-S₂; Mol wt: 582.01

ACTION – Cephem antibiotic proven active against *Staphylococcus aureus* 3004 (MIC = 6.25 µg/ml). Another specifically claimed 3-pyrazoliomethylcephem compound is:



259133: C₂₀-H₂₂-Cl-F-N₈-O₆-S₂

SOURCE – Fujisawa.

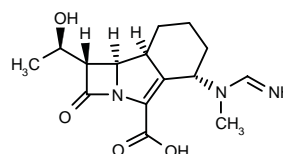
REFERENCES

1. Kawabata, K. et al. (Fujisawa Pharm. Co., Ltd.) *3-Pyrazoliomethylcephem cpds. as antimicrobial agents*. WO 9741128.

GV-129606

259302

(1S,5S,8aS,8bR)-1-[1(R)-Hydroxyethyl]-5-[N-(iminomethyl)-N-methylamino]-2-oxo-1,2,5,6,7,8,8a,8b-octahydroazeto[2,1-a]isoindole-4-carboxylic acid



C₁₅-H₂₁-N₃-O₄; Mol wt: 307.35

ACTION – Potent parenteral trinem antibiotic that combines broad-spectrum activity and high potency and resistance to β-lactamases. It displayed antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria, giving MIC₉₀ values of < 0.015-0.03 µg/ml against penicillin- or methicillin-susceptible staphylococci and streptococci, and 8 µg/ml against methicillin-resistant *Staphylococcus aureus* and vancomycin-susceptible *Enterococcus faecalis*; MIC₉₀ values against Gram-negative bacteria including ceftazidime-resistant isolates and *Pseudomonas aeruginosa* were 0.06-8 µg/ml, and against the anaerobic strains *Clostridium perfringens* and *Bacteroides fragilis* 0.12-0.5 µg/ml. GV-129606 exhibited *in vivo* activity against septicemia in mice caused by Gram-positive (ED₅₀ = 0.05 mg/kg s.c. or less) and Gram-negative bacteria (ED₅₀ = 0.71 mg/kg s.c. or less).

SOURCE – Glaxo Wellcome.

REFERENCES

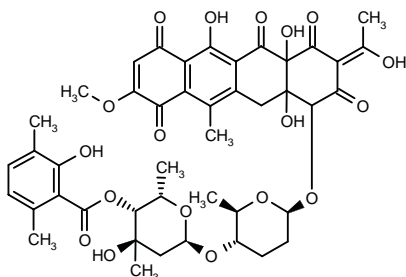
1. Perboni, A. et al. (Glaxo SpA) *Antibacterial condensed carbapenems*. EP 502468, EP 575375, JP 94505018, US 5426104, WO 9215586, WO 9215288.
2. Di Modugno, E. et al. *In vitro and in vivo antibacterial activities of GV129606, a new broad-spectrum trinem*. Antimicrobial Agents Chemother 1997, 41(12): 2742.
3. Pecunioso, A. et al. *Synthesis and enantiomeric excess determination of (6S)-1-(trimethylsilyloxy)-6-(N-methyl-N-benzoyloxycarbonylamino)-cyclohexene*. Tetrahedron Asymmetry 1997, 8(5): 775.

MISCELLANEOUS ANTIBIOTICS

POLYKETOMYCIN

259699

4-[4-[4-[2,6-Dideoxy-4-*O*-(2-hydroxy-3,6-dimethylbenzoyl)-3-*C*-methyl- α -L-*gulo*-hexopyranosyloxy]-2,3,6-trideoxy- β -D-mannopyranosyloxy]-4a,11,12a-trihydroxy-2-(1-hydroxyethylidene)-8-methoxy-6-methyl-1,2,3,4,4a,5,7,10,12,12a-decahydronaphthacene-1,3,7,10,12-pentaone



C44-H48-O18; Mol wt: 864.85

Orange powder.

ACTION – Antibiotic isolated from the culture broth of *Streptomyces* sp. MK277-AF1 (FERM P-15442) with activity against Gram-positive bacteria, giving MIC values of 0.025-0.2 µg/ml against methicillin-sensitive, methicillin-resistant and multidrug-resistant *Staphylococcus aureus*; it also showed antimicrobial activity against *Bacillus subtilis* PC1219 and *Corynebacterium bovis* 1810 (MIC < 0.006 and 0.1 µg/ml, respectively), but had no activity against Gram-positive bacteria (MIC > 100 µg/ml). The compound also exhibited cytotoxic activity against a range of tumor cell lines (IC₅₀ = 2.1, 3.3 and 5.2 µg/ml against EL-4, L1210 and P388 leukemia, respectively; IC₅₀ = 0.9 and 1.0 µg/ml against IMC and Ehrlich carcinoma, respectively; IC₅₀ = 1.5 and 2.4 µg/ml against FS-3 and Meth A fibrosarcoma, respectively; IC₅₀ = 1.6 and 1.8 µg/ml, respectively, against B16-BL10 melanoma and colon 26 adenocarcinoma). The LD₅₀ in mice was estimated to be 6.25-12.5 mg/kg i.p.

SOURCE – Inst. Microbial Chem., Tokyo (JP).

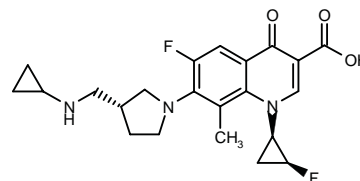
REFERENCES

1. Takeuchi, T. et al. (Inst. Microbial Chem.) *Novel antibiotics, polyketomycine and preparation method thereof*. JP 97301989.
2. Momose, I. et al. *Polyketomycin, a new antibiotic from Streptomyces sp. MK277-AF1 II. Structure determination*. J Antibiot 1998, 51(1): 26.
3. Momose, I. et al. *Polyketomycin, a new antibiotic from Streptomyces sp. MK277-AF1 I. Taxonomy, production, isolation, physico-chemical properties and biological activities*. J Antibiot 1998, 51(1): 21.

MISCELLANEOUS ANTIBACTERIAL DRUGS

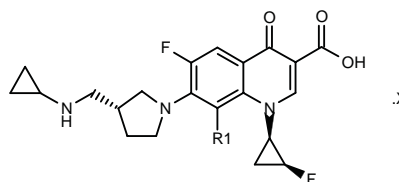
257727

7-[3(*R*)-(Cyclopropylaminomethyl)pyrrolidin-1-yl]-6-fluoro-1-[2(*S*)-fluoro-1(*R*)-cyclopropyl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C22-H25-F2-N3-O3; Mol wt: 417.45

ACTION – Quinolone antibacterial agent with activity against both Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P (MIC = 0.003 µg/ml or less), *Staphylococcus epidermidis* 56500 (MIC = 0.013 µg/ml), *Streptococcus pyogenes* G-36 (MIC = 0.013 µg/ml), *Pseudomonas aeruginosa* 32121 (MIC = 0.10 µg/ml) and *Escherichia coli* NIHJ (MIC = 0.003 µg/ml or less). Other related compounds include the following:



Compound	R1	X	Formula
259967	OMe		C ₂₂ H ₂₆ F ₂ N ₄ O ₄
259968	Me	HCl	C ₂₂ H ₂₆ F ₂ N ₄ O ₃ ·HCl

SOURCE – Daiichi Pharm.

REFERENCES

1. Takemura, M. et al. (Daiichi Pharm. Co., Ltd.) *Cycloalkylaminomethylpyrrolidine derivs*. WO 9740037.

TROVAN™

Trovafloxacin Mesilate

Prop INNM; USAN

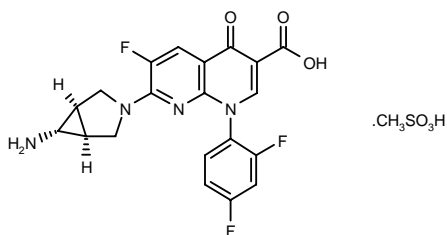
190032

(1 α ,5 α ,6 α)-7-(6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate

7-[(1*R*,5*S*,6*S*)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate

CP-99219⁺

CP-99219-27



C20-H15-F3-N4-O3.C-H4-O3-S; Mol wt: 512.46

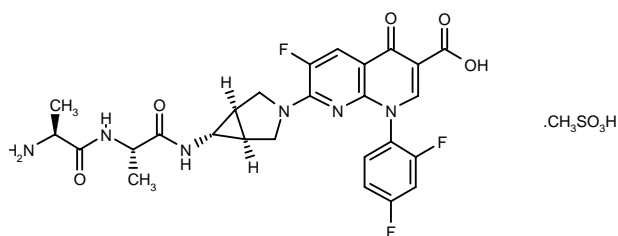
Alatrofloxacin Mesilate

Prop INNM; USAN

210073

(α , α , α)-7-[6-(L-Alanyl-L-alanyl-amino)-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

L-Ala-L-Ala-CP-99219

CP-116517⁺⁺

C26-H25-F3-N6-O5.C-H4-O3-S; Mol wt: 654.62

ACTION – Broad-spectrum fluoronaphthyridine antibacterial agent. Alatrofloxacin mesilate is a prodrug of trovafloxacin that is rapidly converted to the latter after i.v. administration.

INDICATION – Treatment of bacterial infections in adults including bacterial exacerbations of chronic bronchitis, acute sinusitis, community- and hospital-acquired pneumonia, complicated intraabdominal infections, uncomplicated urinary tract infections, pelvic inflammatory disease, chlamydial cervicitis, gonorrhea, skin and skin structure infections and oral prophylactic use in surgery.

PRESENTATION – Single-use vials (40 and 60 ml), 5 mg trovafloxacin/ml as alatrofloxacin mesilate; tablets, 100 and 200 mg trovafloxacin as trovafloxacin mesilate.

PROPRIETARY NAME – Trovan (US).

SOURCE – Pfizer.

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26. Taylor, A. et al. *The effect of varying degrees of renal impairment on the safety, toleration and pharmacokinetics of trovafloxacin*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst A-66.

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32. Vincent, J. et al. *Single- and multiple-dose administration, dosing regimens and the pharmacokinetics of trovafloxacin and alatrofloxacin in man*. 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 2255.

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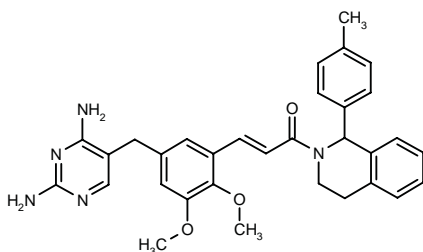
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+Drug Data Rep 1993, 15(1): 86

**Drug Data Rep 1994, 16(11): 1039.

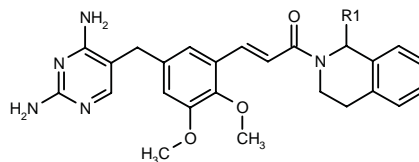
258991

3-[5-(2,4-Diaminopyrimidin-5-ylmethyl)-2,3-dimethoxyphenyl]-1-[1-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-2(*E*)-propan-1-one



C32-H33-N5-O3; Mol wt: 535.64

ACTION – Antibacterial agent active against various microorganisms including multiresistant Gram-positive strains and opportunistic pathogens such as *Pneumocystis carinii* that acts by inhibiting bacterial dihydrofolate reductase (DHFR); compound was very potent against purified DHFR from *Staphylococcus aureus* ATCC 25923, multiresistant *S. aureus* 157/4696 and *P. carinii* (IC_{50} = 0.0002, 0.0048 and 0.33 μ M, respectively, vs. 0.0340, 16.0 and 43.0 μ M, respectively, for trimethoprim). It is reported to exhibit synergistic effects in combination with sulfonamide antibacterial agents. Other compounds from this series of specifically claimed 2,4-diaminopyrimidines include the following:



Compound	R1	Formula
259512	1,3-(Me)2-5-pyrazolyl	C ₃₀ H ₃₃ N ₇ O ₃
259513	cyclopropyl	C ₂₈ H ₃₁ N ₅ O ₃
259514	6-Me-3-Pyr	C ₃₁ H ₃₂ N ₆ O ₃
259515	4-N(Me)2-2-Pyr	C ₃₂ H ₃₅ N ₇ O ₃
259516	4-(NH ₂ CO)-Ph	C ₃₂ H ₃₂ N ₆ O ₄
259517	4-MeS-Ph	C ₃₂ H ₃₃ N ₅ O ₃ S

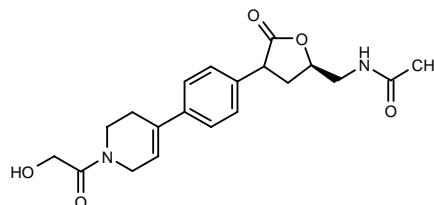
SOURCE – Roche.

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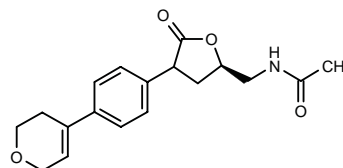
258994

N-[4-[4-[1-(2-Hydroxyacetyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl]-5-oxotetrahydrofuran-2(*R*)-ylmethyl]acetamide



C20-H24-N2-O5; Mol wt: 372.42

ACTION – Antibacterial agent with activity against Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS), including vancomycin-resistant strains, and multiply resistant *Enterococcus faecium* strains. Compound is reported to exhibit a favorable toxicological profile. Another specifically claimed antibiotic compound containing a furanone ring is:



260025: C18-H21-N-O4

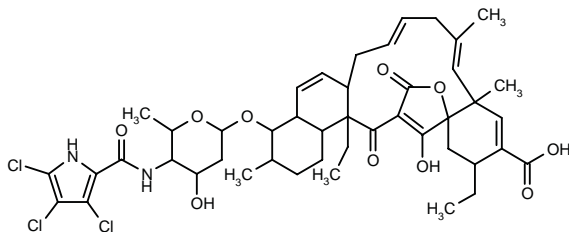
SOURCE – Zeneca.

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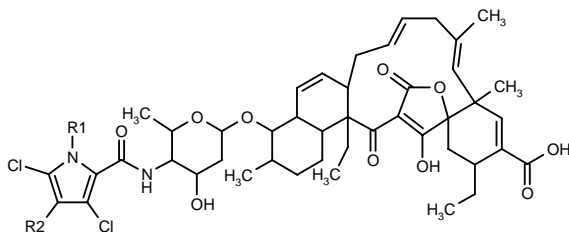
BE-45722B**256436**

15,20a-Diethyl-21-hydroxy-4-[4-hydroxy-6-methyl-5-(3,4,5-trichloro-1*H*-pyrrol-2-ylcarboxamido)tetrahydropyran-2-yloxy]-3,11,12a-trimethyl-18,20-dioxo-2,3,4,4a,6a,7,10,12a,15,16,18,20,20a,20b-tetradecahydro-1*H*-16a,19-methenobenzo[*b*]naphtho[2,1-*j*]oxacyclotetradecine-14-carboxylic acid



C45-H55-Cl3-N2-O10; Mol wt: 890.30

ACTION – Antibacterial agent obtained from *Actinomadura* sp. A45722 (FERM P-1519), active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* strains such as BB6117 (MIC = 0.39 µg/ml) and BB6118 (MIC = 0.20 µg/ml). Other compounds obtained from this source are:



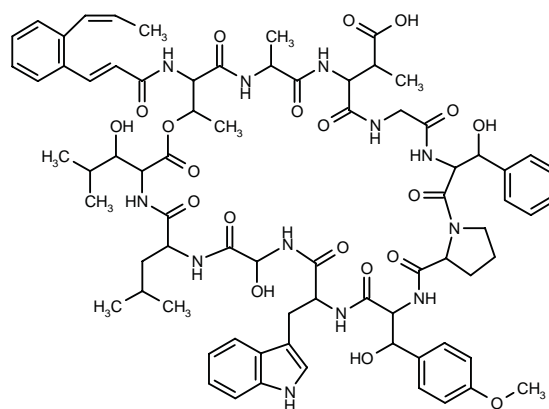
Compound	R1	R2	Formula
BE-45722A [260417]	H	H	C ₄₅ H ₅₆ Cl ₂ N ₂ O ₁₀
BE-45722C [260418]	Me	Cl	C ₄₆ H ₅₇ Cl ₃ N ₂ O ₁₀
BE-45722D [260419]	Me	H	C ₄₆ H ₅₈ Cl ₂ N ₂ O ₁₀

SOURCE – Banyu.**REFERENCES**

1. Torigoe, K. et al. (Banyu Pharm. Co., Ltd.) *Antibacterial substances BE-45722*. JP 97227587.

RP-1776**256437**

2-[9-Hydroxy-3-[1-hydroxy-1-(4-methoxyphenyl)methyl]-15-(1-hydroxy-2-methylpropyl)-31-(1-hydroxy-1-phenylmethyl)-6-(1*H*-indol-3-ylmethyl)-12-isobutyl-18,22-dimethyl-19-[3-[2-[1(*Z*)-propenyl]phenyl]-2(*E*)-propenamido]-1,4,7,10,13,16,20,23,26,29,32-undecaaxoperhydropyrrolo[2,1-*r*][1,4,7,10,13,16,19,22,25,28,31]oxadecaazacyclotetratricontin-25-yl]propionic acid



C75-H94-N12-O20; Mol wt: 1483.64

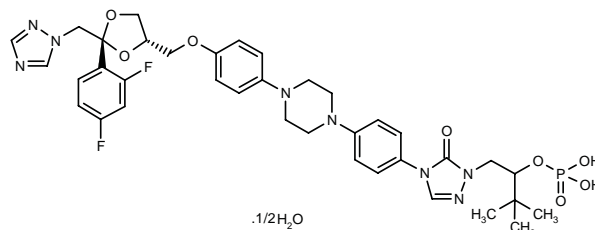
ACTION – Antibacterial agent isolated from *Streptomyces* sp. RP-1776 (FERM BP-5396), proven active *in vitro* against *Staphylococcus aureus* ATCC 6538P (MIC = 277 µM) and *Bacillus subtilis* No. 10707 (MIC = 104 µM).

SOURCE – Kyowa Hakko.**REFERENCES**

1. Doki, S. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Cpd. RP-1776*. JP 97227594.

ANTIFUNGAL AGENTS**258781**

(±)-*cis*-4-[4-[4-[4-[2-(2,4-Difluorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl]piperazin-1-yl]phenyl]-2-[3,3-dimethyl-2-(phosphonoxy)butyl]-3,4-dihydro-2*H*-1,2,4-triazol-3-one hemihydrate



C37-H43-F2-N8-O8-P.1/2H2O; Mol wt: 805.77

ACTION – Water-soluble azole antifungal agent active against a wide variety of fungi such as *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*. It was active at doses below 2.5 mg/kg i.v. in a mouse triple mycosis model in which three mycoses, vaginal candidosis, cutaneous trichophytosis and disseminated aspergillosis, were established simultaneously.

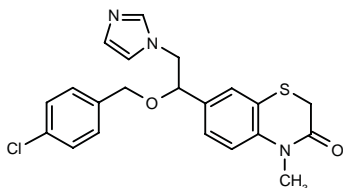
SOURCE – Janssen.

REFERENCES

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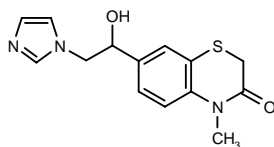
259654

7-[1-(4-Chlorobenzoyloxy)-2-(1-imidazolyl)ethyl]-4-methyl-3,4-dihydro-2H-1,4-benzothiazin-3-one



C21-H20-Cl-N3-O2-S; Mol wt: 413.92

ACTION – Antifungal agent proven active in mice with systemic candidiasis caused by *Candida albicans* strain CA6 (median survival time [MST] > 60 days, 2/10 mice dead at 60 days postinfection at a dose of 10 mg/kg i.p. 2 h before and once daily for 7 days after infection), although it showed only moderate *in vitro* activity against *C. albicans* (MIC = 46 µg/ml). Another azole derivative with activity in this model of systemic candidiasis is:



259979: C14-H15-N3-O2-S

SOURCE – Univ. Perugia, Perugia (IT).

REFERENCES

1. Fringuelli, R. et al. *Azole derivatives of 1,4-benzothiazine as antifungal agents*. Bioorg Med Chem 1998, 6(1): 103.

TEXENOMYCIN A

257187

2-Methyl-3-oxotetradecanoyl-prolyl-(2-aminoisobutyryl)-(2-aminoisobutyryl)-(2-aminoisobutyryl)-(2-aminoisobutyryl)-β-alanyl-alanyl-(2-aminoisobutyryl)-β-alanyl-leucyl-(2-aminoisobutyryl)-β-alanyl-alanyl-(2-aminoisobutyryl)-β-alanyl-alanyl-(2-aminoisobutyryl)-(2-aminoisobutyryl)-alanyl-argininol isomer 1

C97-H170-N24-O23; Mol wt: 2040.56

ACTION – Antifungal agent, a peptide obtained from *Scleroderma texense* DSM 10601, found active against dermatophytes, yeasts and filamentous fungi such as *Trichophyton mentagrophytes* (MIC = 7.81 µg/ml), *Candida albicans* (MIC = 0.24 µg/ml) and *Aspergillus fumigatus* (MIC = 0.24 µg/ml). Another compound from this source is:

2-Methyl-3-oxotetradecanoyl-prolyl-(2-aminoisobutyryl)-(2-aminoisobutyryl)-(2-aminoisobutyryl)-(2-aminoisobutyryl)-alanyl-alanyl-(2-aminoisobutyryl)-β-alanyl-leucyl-(2-aminoisobutyryl)-β-alanyl-alanyl-(2-aminoisobutyryl)-2-(aminoisobutyryl)-(2-aminoisobutyryl)-alanyl-argininol isomer 2

Texenomycin B [259085]: C97-H170-N24-O23

SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Stump, H. et al. (Hoechst AG) *Antifungal peptides from Scleroderma texense*. WO 9736921.

TKR-1912-I

258746

ACTION – Antifungal antibiotic produced by culturing the microorganism *Aureobasidium* sp. TKR1912, proven active against pathogenic fungi including *Candida albicans* TIMM0136 (MIC = 3.13 µg/ml) and *Cryptococcus neoformans* TIMM0354 (MIC = 6.25 µg/ml). No toxicity was observed at 50 mg/kg i.p. in mice. Another compound from this source is:

TKR-1912-II [259303]

SOURCE – Takara Shuzo.

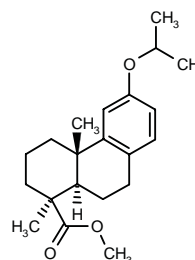
REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Antibiotics TKR1912-I and TKR1912-II and process for producing the same*. EP 814086, WO 9628456.

ANTIVIRAL DRUGS

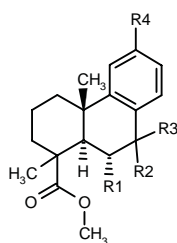
257786

[1S-(1α,4α,10αβ)]-6-Isopropoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid methyl ester



C21-H30-O3; Mol wt: 330.47

ACTION – Antiviral agent capable of inhibiting hemagglutinin-mediated fusion of virus with the host cell; IC₅₀ values were in the range 0.01-32.0 µg/ml for influenza A/Kawasaki/89 and 0.7-97.0 µg/ml for influenza B/Great Lakes in a virus cytopathic effect assay, and in the range 0.006-100.0 µg/ml for influenza A/Kawasaki and 1.47-100.0 µg/ml for influenza B/Great Lakes in a plaque reduction assay. Other related compounds include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
259076	H	H	H	2-(PhCO)-PhO	1S	C ₃₁ H ₃₂ O ₄
259077	H	H	H	1-(t-BuOCO)-4-Pip-COO	1S	C ₂₉ H ₄₁ NO ₆
259078	H	-N[(Me) ₂]-		OMe	1S	C ₂₁ H ₃₀ N ₂ O ₃
259080	Br	-O-		H	1R	C ₁₈ H ₂₁ BrO ₃

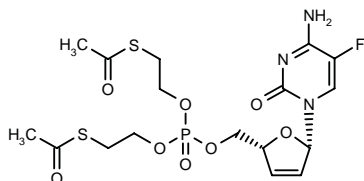
SOURCE – Lilly.

REFERENCES

- Colacino, J.M. et al. (Eli Lilly & Co.) *Anti-viral method*. WO 9741849.
- Hornback, W.J. (Eli Lilly & Co.) *Anti-viral cpds*. EP 806411.

258861

Phosphoric acid *O*¹,*O*²-bis[2-(acetylsulfanyl)ethyl]-*O*³-(β-L-2',3'-didehydro-2',3'-dideoxy-5-fluorocytidin-5'-*O*-yl) tri-ester



C17-H23-F-N3-O8-P-S2; Mol wt: 511.48

$[\alpha]_D^{23} +8.55^\circ$ (c 0.70, MeOH).

ACTION – *S*-Acetyl-2-thioethyl (SATE)-bearing mono-phosphate prodrug of β-L-FD4C with excellent antiviral activity against hepatitis B virus (HBV) *in vitro* using human hepatoblastoma 2.2.15 cells (IC₅₀ = 4 nM for inhibition of HBV DNA synthesis; 90% inhibition at 19 nM), being more active than β-L-FD4C; it was less cytotoxic than the parent compound against human T-cell lymphoblastic leukemia CEM cells (IC₅₀ = 52 μM vs. 13 μM), and was not cytotoxic in other cell lines tested.

SOURCE – Vion Pharm.

REFERENCES

- Li, X. et al. *Bis-S-acyl-2-thioethyl (SATE)-bearing monophosphate prodrug of β-L-FD4C as potent anti-HBV agent*. Bioorg Med Chem Lett 1998, 8(1): 57.

259010

Glutamyl-aspartyl-valyl-valyl-cysteiny-cysteiny-(6-aminohexanoyl)-(6-aminohexanoyl)-lysyl-glycyl-seryl-leucyl-valyl-isoleucyl-arginyl-glycyl-valyl-isoleucyl-valyl-valyl-cysteine

C97-H173-N25-O27-S3; Mol wt: 2217.76

ACTION – Agent for the treatment of hepatitis C that acts by inhibiting hepatitis C virus NS3 protease (IC₅₀ = 0.2 μM). Other representative peptides include the following:

Glutamyl-aspartyl-valyl-valyl-cysteiny-cysteiny-(6-aminohexanoyl)-(6-aminohexanoyl)-cysteiny-valyl-valyl-isoleucyl-valyl-glycyl-arginyl-isoleucyl-valyl-leucyl-seryl-glycyl-lysine

259801; C97-H173-N25-O27-S3

Glutamyl-aspartyl-valyl-valyl-cysteiny-cysteiny-(6-aminohexanoyl)-lysyl-lysyl-glycyl-seryl-leucyl-valyl-isoleucyl-arginyl-glycyl-valyl-isoleucyl-valyl-valyl-cysteine

259802; C97-H174-N26-O27-S3

Glutamyl-aspartyl-valyl-valyl-cysteiny-cysteiny-(6-aminohexanoyl)-lysyl-lysyl-glycyl-seryl-leucyl-valyl-isoleucyl-arginyl-glycyl-valyl-isoleucyl-valyl-valyl-cysteine

259803; C97-H174-N26-O27-S3

Glutamyl-aspartyl-valyl-valyl-cysteiny-cysteiny-(6-aminohexanoyl)-lysyl-glycyl-seryl-leucyl-valyl-isoleucyl-arginyl-glycyl-valyl-isoleucyl-valyl-valyl-cysteiny-lysine

259806; C97-H174-N26-O27-S3

SOURCE – Schering-Plough.

REFERENCES

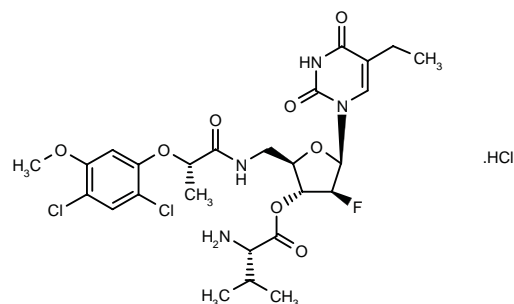
- Zhang, R. et al. (Schering Corp.) *Synthetic inhibitors of hepatitis C virus NS3 protease*. WO 9743310.

RO-32-4397*,¹

250440

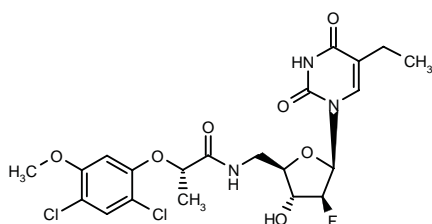
248209 (as free base)

1-[5-[2(*S*)-(2,4-Dichloro-5-methoxyphenoxy)propion-amido]-2,5-dideoxy-2-fluoro-3-*O*-(*L*-valyl)-β-D-arabinofuranosyl]-5-ethyluracil hydrochloride



C26-H33-Cl2-F-N4-O8.HCl; Mol wt: 655.93

ACTION – Antiviral agent, the orally active prodrug of **Ro-32-2313**, a potent and highly selective inhibitor of herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) thymidine kinase ($IC_{50} = 1.8$ and 0.19 nM, respectively) with no activity against cytosolic or mitochondrial enzyme from HeLa cells ($IC_{50} > 10$ μ M). Ro-32-4397 has good oral bioavailability and is active in murine models of HSV-2 infection; it inhibited viral replication in dorsal root ganglia by 75-88% at a dose of 150 mg/kg p.o. 4 times daily x 5 days in a model of latent virus reactivation, it prevented HSV-2-induced lethality in a systemic infection model ($ED_{50} = 75$ mg/kg p.o. b.i.d. x 10 days) and it reduced the severity of skin lesions and increased survival in a zosteriform infection model at doses of 25 and 75 mg/kg p.o. 4 times daily x 10 days.



Ro-32-23132 [248210]:** C21-H24-Cl2-F-N3-O7

SOURCE – Roche.

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4. Mulqueen, M.J. et al. *Viral thymidine kinase is essential for the spread of herpes simplex virus (HSV) induced zosteriform lesions in vivo.* Antivir Res 1997, 34(2): Abst 134.
5. Mulqueen, M.J. et al. *Pharmacological properties of orally active inhibitors of herpes simplex virus (HSV) thymidine kinase.* Antivir Res 1997, 34(2): Abst 19.
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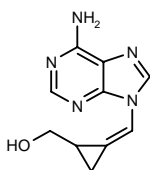
*Identified compound **248209** Drug Data Rep 1997, 19(6): 542.

Identified compound **248210 Drug Data Rep 1997, 19(5): 444.

SYNADENOL

259289

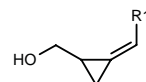
(*Z*)-9-(2-Hydroxymethylcyclopropylidenemethyl)adenosine



C10-H11-N5-O; Mol wt: 217.23

M.p. 238-9 °C.

ACTION – Antiviral agent, a nucleoside analog that has demonstrated activity against a wide range of both herpesviruses and other viruses, although it was less effective against HIV-1. It gave IC_{50} values of 1.0 and 2.1 μ M against human cytomegalovirus (HCMV) and murine cytomegalovirus (MCMV), respectively, 0.2-3.2 μ M against Epstein-Barr virus (EBV), 2.5 μ M against varicella-zoster virus (VZV), 2 μ M against hepatitis B virus (HBV), and 14 μ M against human herpesvirus 6 (HHV-6). In the cytopathic effect inhibition assay, the compound had IC_{50} values against herpes simplex virus type 1 (HSV-1) and (HSV-2) of < 0.14 and 10.6 μ M, respectively. Antiviral activity was observed at noncytotoxic concentrations. Other related compounds are:



Compound	R1	Formula
Synguanol [259300]	guanin-9-yl	C ₁₀ H ₁₁ N ₅ O ₂
259301	2-NH2-6-Cl-purin-9-yl	C ₁₀ H ₁₀ ClN ₅ O

SOURCES – Univ. Alabama Birmingham, Birmingham, AL (US); Univ. Michigan, Ann Arbor, MI (US); Wayne State Univ., Detroit, MI (US); Yale Univ. School Med., New Haven, CT (US).

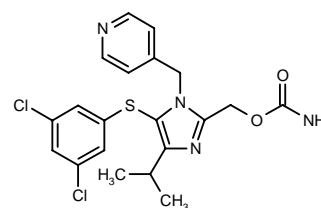
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AIDS MEDICINES

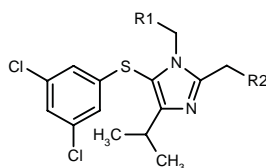
256200

Carbamic acid 5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1-(4-pyridylmethyl)imidazol-2-ylmethyl ester



C20-H20-Cl2-N4-O2-S; Mol wt: 451.37

ACTION – Antiviral agent for AIDS with potent activity against HIV (HTLV-IIIB) in human MOLT-4 T-cells ($EC_{50} = 0.9$ ng/ml), reported to be efficiently absorbed through lymph vessels in the intestinal tract and to migrate to lymph nodes in high concentrations. Other compounds from this series of imidazole derivatives include the following:



Compound	R1	R2	Formula
260437	Me	OH	C ₁₅ H ₁₈ Cl ₂ N ₂ OS
260438	Me	CH ₂ OH	C ₁₆ H ₂₀ Cl ₂ N ₂ OS
260439	Me	1-cyclooctenyl-OCH ₂	C ₂₄ H ₃₂ Cl ₂ N ₂ OS
260440	Me	OCONHAc	C ₁₈ H ₂₁ Cl ₂ N ₃ O ₃ S
260441	4-Pyr	OCONHCH ₂ N(Bu) ₂	C ₂₉ H ₃₉ Cl ₂ N ₅ O ₂ S
260442	4-Pyr	4-morpholinyl-CH ₂ NHCO ₂	C ₂₅ H ₂₉ Cl ₂ N ₅ O ₃ S
260443	4-Pyr	OCONHCH ₂ N(CH ₂ Ph) ₂	C ₃₅ H ₃₅ Cl ₂ N ₅ O ₂ S

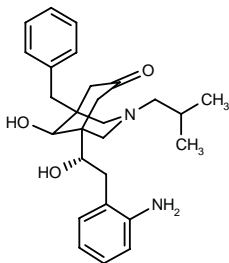
SOURCE – Shionogi.

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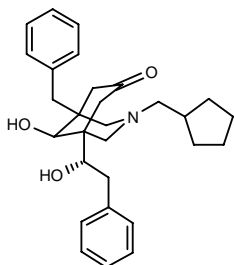
257746

(1*R*,5*S*,9*R*)-1-[2-(2-Aminophenyl)-1-(*S*)-hydroxyethyl]-5-benzyl-9-hydroxy-3-isobutyl-azabicyclo[3.3.1]nonan-7-one



C27-H36-N2-O3; Mol wt: 436.59

ACTION – Antiviral agent for AIDS, an inhibitor of HIV protease (IC₅₀ = 1.6 μM). Another specifically claimed compound is:



259125: C29-H37-N-O3

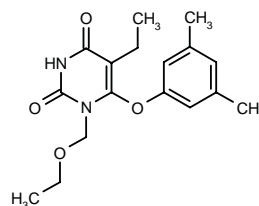
SOURCE – Merck & Co.

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1. Coburn, C.A. et al. (Merck & Co., Inc.) *HIV protease inhibitors useful for the treatment of AIDS.* WO 9740833.

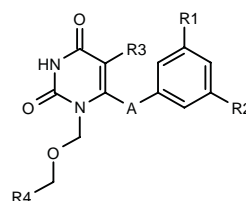
258985

6-(3,5-Dimethylphenoxy)-1-(ethoxymethyl)-5-ethylpyrimidine-2,4(1*H*,3*H*)-dione



C17-H22-N2-O4; Mol wt: 318.37

ACTION – Antiviral agent for AIDS with potent *in vitro* activity against HIV-1 in infected MT-4 cells (ED₅₀ < 0.001 μg/ml) and low cytotoxic potential (CD₅₀ = 84.68 μg/ml in uninfected cells; selectivity index [CD₅₀/ED₅₀] > 84,680). Within this series of 2,4-pyrimidinedione derivatives, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
259327	H	H	Et	Me	O	C ₁₅ H ₁₈ N ₂ O ₄
259328	Me	Me	Et	Ph	O	C ₂₂ H ₂₄ N ₂ O ₄
259329	H	H	i-Pr	Ph	O	C ₂₁ H ₂₂ N ₂ O ₄
259330	Me	Me	i-Pr	CH ₂ OAc	O	C ₂₀ H ₂₆ N ₂ O ₆
259331	Me	Me	i-Pr	CH ₂ OH	O	C ₁₈ H ₂₄ N ₂ O ₅
259332	Me	Me	i-Pr	CH ₂ OMe	O	C ₁₉ H ₂₆ N ₂ O ₅
259333	Me	Me	i-Pr	Me	CO	C ₁₉ H ₂₄ N ₂ O ₄
259334	Me	Me	Et	Ph	CO	C ₂₃ H ₂₄ N ₂ O ₄
259335	Me	Me	Et	CH ₂ OMe	CO	C ₁₉ H ₂₄ N ₂ O ₅

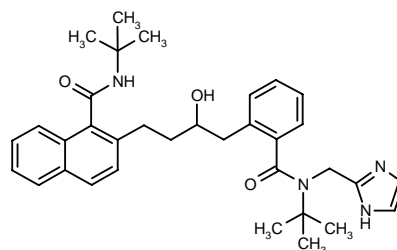
SOURCES – Korea Res. Inst. Chem. Technol., Daejeon (KR); Samjin.

REFERENCES

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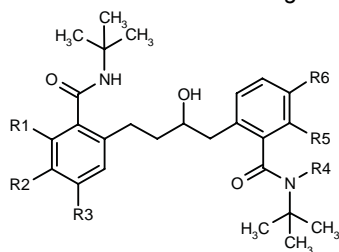
259726

N-*tert*-Butyl-2-[4-[1-(*N*-*tert*-butylcarbamoyl)-2-naphthyl]-2-hydroxybutyl]-*N*-(2-imidazolyl)benzamide

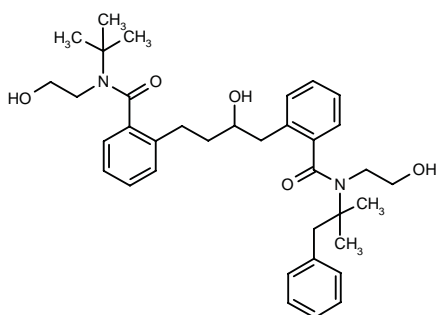


C34-H42-N4-O3; Mol wt: 554.73

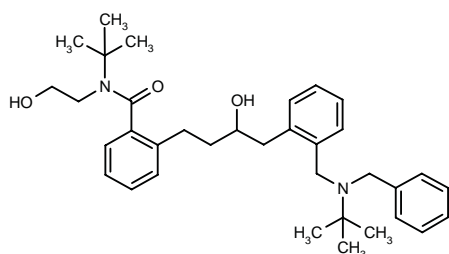
ACTION – Antiviral agent for AIDS with HIV protease-inhibitory activity ($IC_{50} = 0.82 \mu M$; $K_i = 0.79 \mu M$). Other related compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
260000	H	t-Bu	H	H	-CH=CHCH=CH-		$C_{34}H_{46}N_2O_3$
260001	-CH=CHCH=CH-		H	H	-CH=CHCH=CH-		$C_{34}H_{40}N_2O_3$
260002	H	t-Bu	H	CH ₂ -CH ₂ OH	H	H	$C_{32}H_{48}N_2O_4$
260003	-CH=CHCH=CH-		H	H	-CH=CHCH=CH-		$C_{34}H_{40}N_2O_3$
260004	H	-CH=CHCH=CH-		CH ₂ -CH ₂ OH	H	H	$C_{32}H_{42}N_2O_4$



260005: C₃₆-H₄₈-N₂-O₅



260006: C₃₅-H₄₈-N₂-O₃

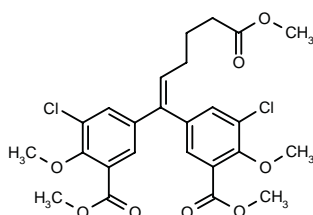
SOURCE – Agouron.

REFERENCES

1. Reich, S.H. et al. (Agouron Pharm.) *HIV protease inhibitors and methods of making the same*. US 5714518, WO 9415906.

259752

6,6-Bis[3-chloro-4-methoxy-5-(methoxycarbonyl)phenyl]-6-hexenoic acid methyl ester



C₂₅-H₂₆-Cl₂-O₈; Mol wt: 525.38

Pale yellow oil.

ACTION – Non-nucleoside HIV-1 reverse transcriptase inhibitor with enhanced potency compared to other previously described alkenyldiarylmethane (ADAM) analogs. It displays an IC_{50} of $0.3 \mu M$ for the enzyme using poly(rC)oligo(dG) as the template/primer and an EC_{50} for preventing the cytopathic effect of HIV-1_{RF} in CEM-SS cells of $13 nM$, whereas the CC_{50} for cytotoxicity in uninfected CEM-SS cells was $31.6 \mu M$, giving a therapeutic index (CC_{50}/EC_{50}) of 2430.

SOURCES – Natl. Cancer Inst.-Frederick Cancer Res. Dev. Cent., Frederick, MD (US); Purdue Univ., West Lafayette, IN (US).

REFERENCES

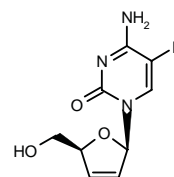
1. Cushman, M. et al. *Synthesis of a non-nucleoside reverse transcriptase inhibitor in the alkenyldiarylmethane (ADAM) series with optimized potency and therapeutic index*. Bioorg Med Chem Lett 1998, 8(2): 195.

β-D-D4FC

260501

β-D-2',3'-Didehydro-2',3'-dideoxy-5-fluorocytidine

D-D4FC



C₉-H₁₀-F-N₃-O₃; Mol wt: 227.19

ACTION – Antiviral cytosine nucleoside active against HIV-1 and hepatitis B virus (HBV) at submicromolar concentrations ($EC_{50} = 0.003 \mu M$ against HBV in 2.2.15 cells) and lacking the cytotoxicity of the β-L-enantiomer. The triphosphate was a potent and selective inhibitor of recombinant HIV-1 reverse transcriptase ($IC_{50} = 0.28 \mu M$) and also exhibited good activity against woodchuck hepatitis virus DNA polymerase and reverse transcriptase; it retained potency against a mutant HIV-1 reverse transcriptase (M184V) and was not crossresistant with (–)-FTC or 3TC, in contrast to the β-L-enantiomer. The compound was orally bioavailable in monkeys ($F = 48\%$), with a terminal elimination half-life of about 4 h, and was mainly cleared by the kidney.

SOURCES – Univ. Alabama, Birmingham, AL (US); Emory Univ., Atlanta, GA (US).

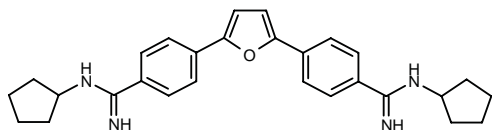
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1. Schinazi, R.F. and Liotta, D.C. (Emory Univ.) *[5-Carboxamido or 5-fluoro]-[2',3'-unsaturated or 3'-modified]-pyrimidine nucleosides*. EP 805683, US 5703058, WO 9622778.
2. Faraj, A. et al. *Effects of β-D-2',3'-didehydro-2',3'-dideoxy-5-fluorocytidine 5'-triphosphate (β-D-D4FC-TP) and its β-L-enantiomer 5'-triphosphate (β-L-D4FC-TP) on viral DNA polymerases*. Antivir Res 1997, 34(2): A66.
3. Schinazi, R.F. et al. *Nucleosides with dual anti-HIV and HBV activity*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 629.
4. Sommadossi, J-P. et al. *Effect of β-enantiomeric and racemic nucleoside analogues on mitochondrial functions in HepG2 cells*. Antivir Res 1997, 34(2): A52.

TREATMENT OF PROTOZOAL DISEASES

259299

4,4'-(2,5-Furandiyl)bis[*N*-cyclopentylbenzenecarboximidamide]



C28-H32-N4-O; Mol wt: 440.59

Pale yellow solid, m.p. 200-1 °C; dihydrochloride, yellow solid, m.p. 294-6 °C (decomp.).

ACTION – Antiprotozoal agent with strong affinity for DNA that also shows some cytotoxic activity against cisplatin-sensitive and -resistant human ovarian tumor cells. The agent was approximately 100 times more potent than pentamidine in the immunosuppressed rat model of *Pneumocystis carinii* pneumonia.

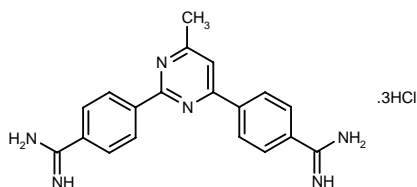
SOURCES – Georgia State Univ., Atlanta, GA (US); Univ. North Carolina Chapel Hill, Chapel Hill, NC (US).

REFERENCES

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2. Neidle, S. et al. Cytotoxicity of bis(phenylamidinium)furan alkyl derivatives in human tumour cell lines: Relation to DNA minor groove binding. *Bioorg Med Chem Lett* 1997, 7(11): 1403.

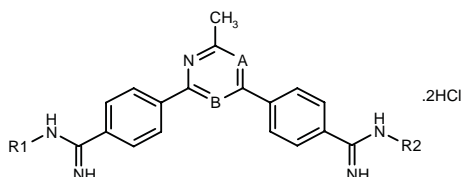
259449

4,4'-(6-Methylpyrimidin-2,4-diyl)bis(benzenecarboximidamide) trihydrochloride



C19-H18-N6.3HCl; Mol wt: 439.77

ACTION – Antiprotozoal agent with strong affinity for DNA, proven to be more active and less toxic than pentamidine in the immunosuppressed rat model of *Pneumocystis carinii* pneumonia. Other dicationic diaryl methylpyrimidines with a similar profile are:



Compound	R1=R2	A	B	Formula
259450	i-Pr	CH	N	C ₁₉ H ₁₈ N ₆ .2HCl
259451	H	N	CH	C ₁₉ H ₁₈ N ₆ .2HCl

SOURCES – Georgia State Univ., Atlanta, GA (US); Univ. North Carolina Chapel Hill, Chapel Hill, NC (US).

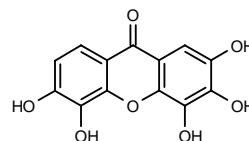
REFERENCES

1. Boykin, D.W. et al. Anti-*Pneumocystis carinii* pneumonia activity of dicationic diaryl methylpyrimidines. *Eur J Med Chem* 1997, 32(12): 965.

260505

2,3,4,5,6-Pentahydroxy-9*H*-xanthen-9-one

2,3,4,5,6-Pentahydroxyxanthone



C13-H8-O7; Mol wt: 276.20

ACTION – Antimalarial agent that inhibits the growth of both chloroquine-sensitive (D6) and multidrug-resistant (W2) strains of *Plasmodium falciparum* *in vitro* (IC₅₀ = 0.4 ± 0.1 and 0.3 ± 0.1 μM, respectively); it is thought to exert its antimalarial action by preventing hemozoin formation, as indicated by inhibition of heme polymerization *in vitro* (IC₅₀ = 1.2 μM).

SOURCES – Interlab.

REFERENCES

1. Winter, R.W. et al. (Interlab Corp.) Xanthone analogs for the treatment of infectious diseases. WO 9734482.
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3. Ignatushchenko, M.V. et al. Xanthoness as antimalarial agents; studies of a possible mode of action. *FEBS Lett* 1997, 409(1): 67.
4. Winter, R.W. et al. Potentiation of an antimalarial oxidant drug. *Antimicrob Agents Chemother* 1997, 41(7): 1449.

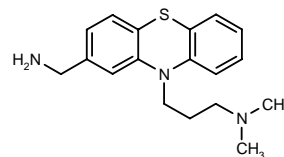
CC201

259692

2-(Aminomethyl)-10-[3-(dimethylamino)propyl]phenothiazine

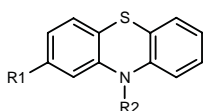
2-(Aminomethyl)-*N,N*-dimethyl-10*H*-phenothiazine-10-propanamine

79009



C18-H23-N3-S; Mol wt: 313.46

ACTION – Selective and reversible trypanothione reductase inhibitor ($I_{50} = 219 \pm 13 \mu\text{M}$ using recombinant enzyme from *Trypanosoma cruzi*) that exhibits strong activity *in vitro* against *Trypanosoma brucei* ($ED_{50} = 0.37 \mu\text{M}$). However, it was toxic to host cells (macrophages) when tested against both *Leishmania donovani* and *T. cruzi*. Other phenothiazines with a similar pharmacological profile are:



Compound	R1	R2	Formula
CC112 [259693]	C(Me)=NOCH2Ph	(CH2)3N(Me)2	C ₂₆ H ₂₉ N ₃ OS
CC127 [259694]	Cl	COCH2Br	C ₁₄ H ₉ BrClNOS

SOURCES – Univ. Dundee, Dundee (GB); London School Hygiene Trop. Med., London (GB); Univ. Manchester, Manchester (GB).

REFERENCES

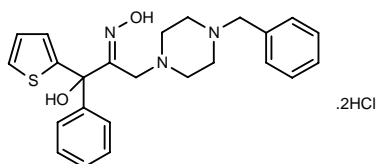
- Chan, C. et al. Phenothiazine inhibitors of trypanothione reductase as potential anti-trypanosomal and antileishmanial drugs. J Med Chem 1998, 41(2): 148.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

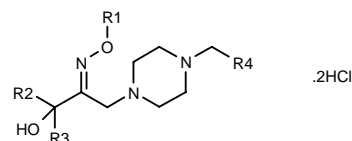
256433

1-(4-Benzylpiperazin-1-yl)-3-hydroxy-3-phenyl-3-(2-thienyl)-2-propanone oxime dihydrochloride



C₂₄-H₂₇-N₃-O₂-S.2HCl; Mol wt: 494.48

ACTION – Antiarthritic agent also claimed for the treatment of cancer metastasis, periodontal disease and corneal ulcers, an inhibitor of matrix metalloproteinases (MMPs) such as collagenase ($IC_{50} = 0.27 \mu\text{M}$ using enzyme from human fibroblasts), MMP-2 (progelatinase A; $IC_{50} = 0.047 \mu\text{M}$) and MMP-9 (progelatinase B; $IC_{50} = 8.0 \mu\text{M}$). Within this series of oxime derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
260422	H	Ph	Ph	Pr	C ₂₃ H ₃₁ N ₃ O ₂ .2HCl
260423	H	Ph	Ph	Pr	C ₂₆ H ₂₉ N ₃ O ₂ .2HCl
260424	Me	Ph	Ph	Pr	C ₂₇ H ₃₁ N ₃ O ₂ .2HCl
260425	Ac	Ph	Ph	Pr	C ₂₈ H ₃₁ N ₃ O ₂ .2HCl
260426	H	Ph	Ph	4-(CO2Me)-Ph	C ₂₈ H ₃₁ N ₃ O ₄ .2HCl
260427	H	Ph	Ph	4-CO2H-Ph	C ₂₇ H ₂₉ N ₃ O ₄ .2HCl
260428	H	4-Me-Ph	2-thienyl	Pr	C ₂₈ H ₂₉ N ₃ O ₂ .2HCl
260429	H	2-thienyl	2-thienyl	Pr	C ₂₂ H ₂₅ N ₃ O ₂ .2HCl
260430	H	CH2CH2Ph	CH2CH2Ph	Pr	C ₃₀ H ₃₇ N ₃ O ₂ .2HCl

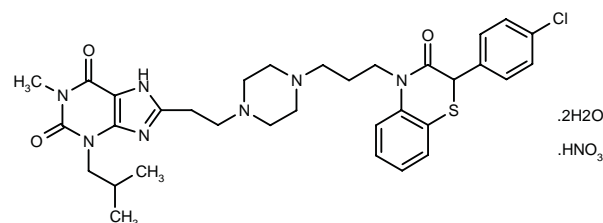
SOURCE – Kotobuki.

REFERENCES

- Tomiyama, T. et al. (Kotobuki Seiyaku Co., Ltd.) Oxime derivs., the preparation method thereof, and medicinal compsns. containing the same. JP 9727539.

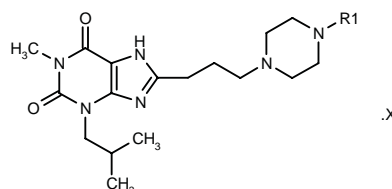
256435

8-[2-[4-[3-[2-(4-Chlorophenyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl]propyl]piperazin-1-yl]ethyl]-3-isobutyl-1-methylxanthine nitrate dihydrate



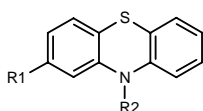
C₃₃-H₄₀-Cl-N₇-O₃-S.H-N-O₃.2H₂O; Mol wt: 749.28

ACTION – Antiinflammatory agent with NFκB-inhibitory activity, proven to inhibit phytohemagglutinin-stimulated IL-2 production in human Jurkat T-cells (91.2% inhibition at 10 μM). A representative compound from a series of xanthine derivatives, wherein the following are also included:



Compound	R1	X	Formula
260395	3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl-(CH2)3	fumarate ethanolate	C ₂₈ H ₃₉ N ₇ O ₃ S .C ₄ H ₄ O ₄ .C ₂ H ₆ O
260396	3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl		C ₂₅ H ₃₃ N ₇ O ₃ S
260397	2-(4-Cl-Ph)-3-oxo-3,4-dihydro-2H-1,4-benzoxacin-4-yl-(CH2)3	difumarate	C ₃₄ H ₄₂ ClN ₇ O ₄ .2C ₄ H ₄ O ₄
260398	2-(4-Cl-Ph)-4-oxo-3,4-dihydro-2H-1,3-benzothiazin-3-yl-(CH2)3	difumarate hydrate	C ₃₄ H ₄₂ ClN ₇ O ₅ S .2C ₄ H ₄ O ₄ .H ₂ O
260399	2-oxo-1,2-dihydro-1-quinolyl-(CH2)3	H ₂ O	C ₂₉ H ₃₉ N ₇ O ₃ .H ₂ O
260401	2-oxo-3,4-dihydro-2H-3-benzothiazolyl-(CH2)3	difumarate hydrate	C ₂₇ H ₃₇ N ₇ O ₃ S .2C ₄ H ₄ O ₄ .H ₂ O

ACTION – Selective and reversible trypanothione reductase inhibitor ($I_{50} = 219 \pm 13 \mu\text{M}$ using recombinant enzyme from *Trypanosoma cruzi*) that exhibits strong activity *in vitro* against *Trypanosoma brucei* ($ED_{50} = 0.37 \mu\text{M}$). However, it was toxic to host cells (macrophages) when tested against both *Leishmania donovani* and *T. cruzi*. Other phenothiazines with a similar pharmacological profile are:



Compound	R1	R2	Formula
CC112 [259693]	C(Me)=NOCH2Ph	(CH2)3N(Me)2	C ₂₆ H ₂₉ N ₃ OS
CC127 [259694]	Cl	COCH2Br	C ₁₄ H ₉ BrClNOS

SOURCES – Univ. Dundee, Dundee (GB); London School Hygiene Trop. Med., London (GB); Univ. Manchester, Manchester (GB).

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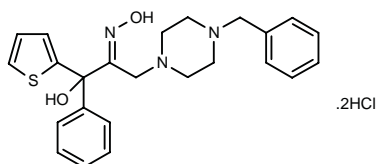
1. Chan, C. et al. Phenothiazine inhibitors of trypanothione reductase as potential anti-trypanosomal and antileishmanial drugs. J Med Chem 1998, 41(2): 148.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

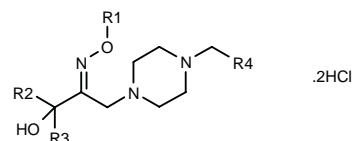
256433

1-(4-Benzylpiperazin-1-yl)-3-hydroxy-3-phenyl-3-(2-thienyl)-2-propanone oxime dihydrochloride



C₂₄-H₂₇-N₃-O₂-S.2HCl; Mol wt: 494.48

ACTION – Antiarthritic agent also claimed for the treatment of cancer metastasis, periodontal disease and corneal ulcers, an inhibitor of matrix metalloproteinases (MMPs) such as collagenase ($IC_{50} = 0.27 \mu\text{M}$ using enzyme from human fibroblasts), MMP-2 (progelatinase A; $IC_{50} = 0.047 \mu\text{M}$) and MMP-9 (progelatinase B; $IC_{50} = 8.0 \mu\text{M}$). Within this series of oxime derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
260422	H	Ph	Ph	Pr	C ₂₃ H ₃₁ N ₃ O ₂ .2HCl
260423	H	Ph	Ph	Pr	C ₂₆ H ₂₉ N ₃ O ₂ .2HCl
260424	Me	Ph	Ph	Pr	C ₂₇ H ₃₁ N ₃ O ₂ .2HCl
260425	Ac	Ph	Ph	Pr	C ₂₈ H ₃₁ N ₃ O ₂ .2HCl
260426	H	Ph	Ph	4-(CO2Me)-Ph	C ₂₈ H ₃₁ N ₃ O ₄ .2HCl
260427	H	Ph	Ph	4-CO2H-Ph	C ₂₇ H ₂₉ N ₃ O ₄ .2HCl
260428	H	4-Me-Ph	2-thienyl	Pr	C ₂₈ H ₂₉ N ₃ O ₂ S.2HCl
260429	H	2-thienyl	2-thienyl	Pr	C ₂₂ H ₂₅ N ₃ O ₂ S ₂ .2HCl
260430	H	CH2CH2Ph	CH2CH2Ph	Pr	C ₃₀ H ₃₇ N ₃ O ₂ .2HCl

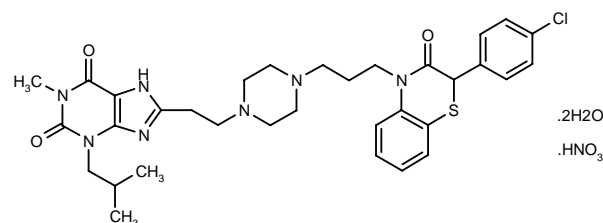
SOURCE – Kotobuki.

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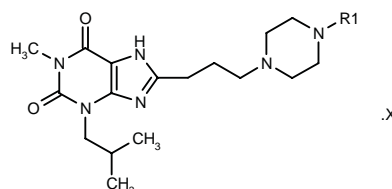
256435

8-[2-[4-[3-[2-(4-Chlorophenyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl]propyl]piperazin-1-yl]ethyl]-3-isobutyl-1-methylxanthine nitrate dihydrate

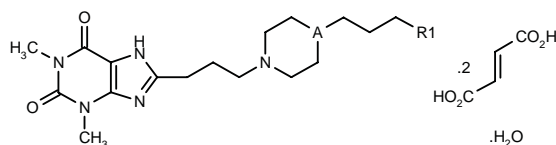


C₃₃-H₄₀-Cl-N₇-O₃-S.H-N-O₃.2H₂O; Mol wt: 749.28

ACTION – Antiinflammatory agent with NFκB-inhibitory activity, proven to inhibit phytohemagglutinin-stimulated IL-2 production in human Jurkat T-cells (91.2% inhibition at 10 μM). A representative compound from a series of xanthine derivatives, wherein the following are also included:



Compound	R1	X	Formula
260395	3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl-(CH2)3	fumarate ethanolate	C ₂₈ H ₃₉ N ₇ O ₃ S .C ₄ H ₄ O ₄ .C ₂ H ₆ O
260396	3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl		C ₂₅ H ₃₃ N ₇ O ₃ S
260397	2-(4-Cl-Ph)-3-oxo-3,4-dihydro-2H-1,4-benzoxacin-4-yl-(CH2)3	difumarate	C ₃₄ H ₄₂ ClN ₇ O ₄ .2C ₄ H ₄ O ₄
260398	2-(4-Cl-Ph)-4-oxo-3,4-dihydro-2H-1,3-benzothiazin-3-yl-(CH2)3	difumarate hydrate	C ₃₄ H ₄₂ ClN ₇ O ₅ S .2C ₄ H ₄ O ₄ .H ₂ O
260399	2-oxo-1,2-dihydro-1-quinolyl-(CH2)3	H ₂ O	C ₂₉ H ₃₉ N ₇ O ₃ .H ₂ O
260401	2-oxo-3,4-dihydro-2H-3-benzothiazolyl-(CH2)3	difumarate hydrate	C ₂₇ H ₃₇ N ₇ O ₃ S .2C ₄ H ₄ O ₄ .H ₂ O



Compound	R1	A	Formula
260403	2-(4-Cl-Ph)-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-4-yl	CH	C ₃₂ H ₃₇ ClN ₆ O ₃ S .2C ₄ H ₄ O ₄ .H ₂ O
260404	2-(4-Cl-Ph)-4-oxo-3,4-dihydro-2H-1,3-benzothiazin-3-yl	N	C ₃₁ H ₃₆ ClN ₇ O ₃ S .2C ₄ H ₄ O ₄ .H ₂ O

SOURCE – Tanabe Seiyaku.

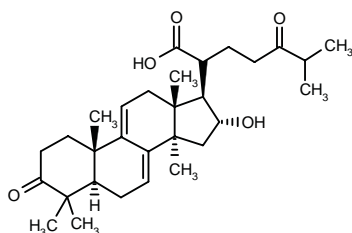
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256445

16 α -Hydroxy-3,24-dioxo-21-nor-5 α -7,9(11)-lanostadiene-20-carboxylic acid

16 α -Hydroxy-4,4,14-trimethyl-3,24-dioxo-21-nor-5 α -7,9(11)-cholestadiene-20-carboxylic acid



C30-H44-O5; Mol wt: 484.67

ACTION – Triterpene derivative isolated from *Daedalea dickinsi*, with collagenase-inhibitory activity and potential in the treatment of a variety of diseases including rheumatoid arthritis, periodontal disease, bone resorption and corneal ulcers.

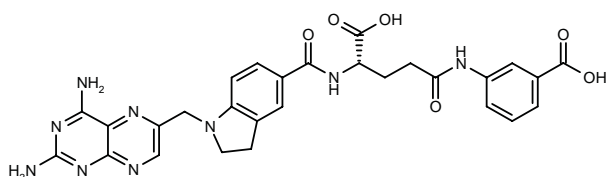
SOURCE – Kanebo.

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256863

3-[4(*S*)-Carboxy-4-[1-(2,4-diaminopteridin-6-ylmethyl)-2,3-dihydro-1*H*-indol-5-ylcarboxamido]butyramido]benzoic acid



C28-H27-N9-O6; Mol wt: 585.58

Orange powder.

ACTION – Antiarthritic agent, a glutamate derivative with potent antiproliferative activity against human peripheral blood mononuclear cells (hPBMC) *in vitro* (IC₅₀ = 12 nM

for hPBMC from healthy volunteers; IC₅₀ methotrexate = 24 nM) but less active than methotrexate against human synovial cells (hSC) from patients with rheumatoid arthritis (IC₅₀ = 540 nM vs. 61 nM).

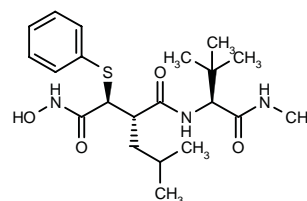
SOURCE – Chugai.

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3. Matsuoka, H. et al. *Antirheumatic agents. III Novel methotrexate derivatives bearing an indoline ring and a modified ornithine or glutamic acid.* Chem Pharm Bull 1997, 45(7): 1146.

257805

N-[4-(Hydroxyamino)-2(*S*)-isobutyl-3(*S*)-(phenylsulfanyl)-succinyl]-*L*-*tert*-leucine methylamide



C21-H33-N3-O4-S; Mol wt: 423.57

ACTION – Antiarthritic agent that acts as an inhibitor of the production of tumor necrosis factor (TNF) and of matrix metalloproteinases (MMPs) such as stromelysin, collagenase and gelatinase. In particular, the compound gave an IC₅₀ value of 0.8 nM against proTNF- α convertase and inhibited TNF- α production in a human myelomonocytic cell line and in whole blood at concentrations below 50 μ M. A compound within a series of specifically claimed thio derivatives of hydroxamic acids.

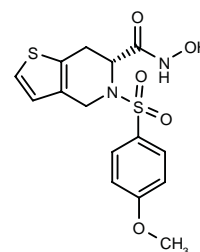
SOURCE – Zeneca.

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1. Bird, T.G.C. et al. (Zeneca, Ltd.; Zeneca Pharma.) *Thio derivs. of hydroxamic acids.* WO 9742168.

258581

5-(4-Methoxyphenylsulfonyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-6(*R*)-carboxhydroxamic acid



C15-H16-N2-O5-S2; Mol wt: 368.42

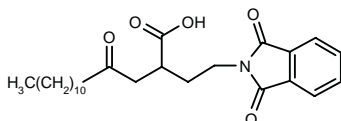
SOURCE – Bayer.

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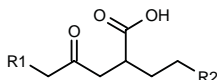
258973

4-Oxo-2-(2-phthalimidoethyl)pentadecanoic acid



C25-H35-N-O5; Mol wt: 429.56

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases (MMPs), particularly MMP-3 (human stromelysin; IC₅₀ = 2950 μM), MMP-9 (human recombinant progelatinase B; IC₅₀ = 91 μM) and MMP-2 (human recombinant progelatinase A; IC₅₀ = 750 μM). Also claimed for the treatment of other conditions involving MMPs such as tumor metastasis and osteopenias. Within this series of substituted oxobutyric acids, the following are also included:



Compound	R1	R2	Formula
259821	C9H19	1,3-dioxo-2-isoindoliny	C ₂₄ H ₃₃ NO ₅
259822	C8H17	1,3-dioxo-2-isoindoliny	C ₂₃ H ₃₁ NO ₅
259823	C11H23	1,3-dioxo-2-isoindoliny	C ₂₆ H ₃₇ NO ₅
259824	C12H25	1,3-dioxo-2-isoindoliny	C ₂₇ H ₃₉ NO ₅
259825	C13H27	1,3-dioxo-2-isoindoliny	C ₂₈ H ₄₁ NO ₅
259826	CH2CH2Ph	Ph	C ₂₁ H ₂₄ O ₃
259827	CH2Ph	Ph	C ₂₀ H ₂₂ O ₃
259828	Ph	Ph	C ₁₉ H ₂₀ O ₃

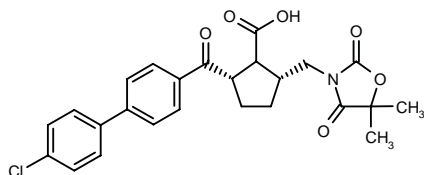
SOURCE – Bayer.

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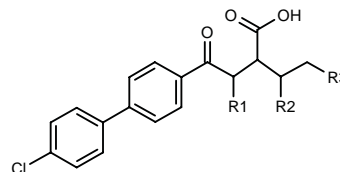
258974

2α-(4'-Chlorobiphenyl-4-ylcarbonyl)-5α-(5,5-dimethyl-2,4-dioxooxazolidin-3-ylmethyl)cyclopentane-1-carboxylic acid



C25-H24-Cl-N-O6; Mol wt: 469.92

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases (MMPs), particularly MMP-3 (human stromelysin; IC₅₀ = 14 nM), MMP-9 (human recombinant progelatinase B; IC₅₀ = 110 nM) and MMP-2 (human recombinant progelatinase A; IC₅₀ = 10 nM). Also claimed for the treatment of other conditions involving MMPs such as tumor metastasis and osteopenias. Other representative compounds within this series of substituted biaryl oxobutyric acid derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
259772	-CH2-	-CH2-	4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl	2α,5α	C ₂₇ H ₂₂ ClN ₃ O ₄
259773	-CH2-	-CH2-	OCH2OCH2Ph	2α,5α	C ₂₈ H ₂₇ ClO ₅
259774	-CH2-	-CH2-	1-pyrrolidinyl-CSS	2α,5α	C ₂₅ H ₂₆ ClNO ₃ S ₂
259775	-CH2-	-CH2-	1,1,3-trioxo-1,3-dihydro-2H-1,2-benzisothiazol-2-yl	2α,5α	C ₂₇ H ₂₂ ClNO ₆ S
259776	-CH2-	-CH2-	1-oxo-1,2-dihydro-2-phthalazinyl	2α,5α	C ₂₈ H ₂₃ ClN ₂ O ₄
259777	-CH2-	-CH2-	2-oxo-2,3-dihydro-3-benzoxazolyl	2α,5α	C ₂₇ H ₂₂ ClNO ₅
259778	-CH2-	-CH2-	2,4-dioxo-3-thiazolidinyl	2α,5α	C ₂₃ H ₂₀ ClNO ₅ S
259779	H	H	1-oxo-1,2-dihydro-2-phthalazinyl		C ₂₆ H ₂₁ ClN ₂ O ₄
259780	H	H	4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl		C ₂₅ H ₂₀ ClN ₃ O ₄
259781	H	H	4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl	R*	C ₂₅ H ₂₀ ClN ₃ O ₄

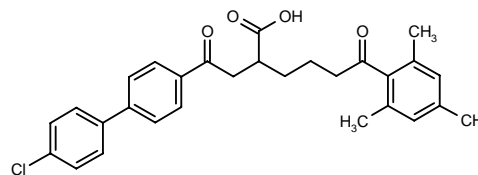
SOURCE – Bayer.

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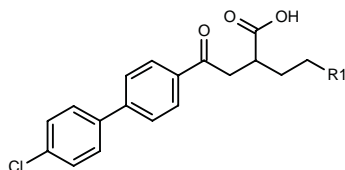
258975

2-[2-(4'-Chlorobiphenyl-4-yl)-2-oxoethyl]-6-oxo-6-(2,4,6-trimethylphenyl)hexanoic acid



C29-H29-Cl-O4; Mol wt: 477.00

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases (MMPs), particularly MMP-3 (human stromelysin; IC₅₀ = 39.6 μM), MMP-9 (human recombinant progelatinase B; IC₅₀ = 1310 μM) and MMP-2 (human recombinant progelatinase A; IC₅₀ = 30.8 μM). Also claimed for the treatment of other conditions involving MMPs such as tumor metastasis and osteopenias. Other representative compounds within this series of 2-(ω-aryl-alkyl)-4-biaryl-oxobutyric acids include the following:



Compound	R1	Formula
259788	CH ₂ COPh	C ₂₆ H ₂₃ ClO ₄
259789	COPh	C ₂₅ H ₂₁ ClO ₄
259790	CH ₂ CH ₂ COPh	C ₂₇ H ₂₅ ClO ₄
259791	(CH ₂) ₃ COPh	C ₂₈ H ₂₇ ClO ₄
259792	2,4,6-(MeO) ₃ -PhCOCH ₂	C ₂₉ H ₂₉ ClO ₇
259793	4-PhO-PhCOCH ₂	C ₃₂ H ₂₇ ClO ₅
259794	4-Me-PhCOCH ₂	C ₂₇ H ₂₅ ClO ₄
259795	4-Br-PhCOCH ₂	C ₂₆ H ₂₂ BrClO ₄
259796	4-MeO-PhCOCH ₂	C ₂₇ H ₂₅ ClO ₅
259797	3,4-(Me) ₂ -PhCOCH ₂	C ₂₈ H ₂₇ ClO ₄
259798	2,4-(MeO) ₂ -PhCOCH ₂	C ₂₈ H ₂₇ ClO ₆
259799	4-t-Bu-PhCOCH ₂	C ₃₀ H ₃₁ ClO ₄
259800	4-Et-PhCOCH ₂	C ₂₈ H ₂₇ ClO ₄
260793	4-i-Pr-PhCOCH ₂	C ₂₉ H ₂₉ ClO ₄

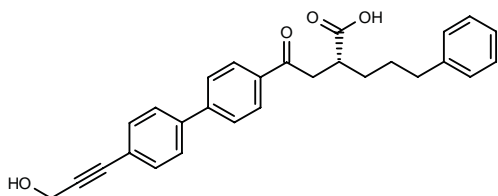
SOURCE – Bayer.

REFERENCES

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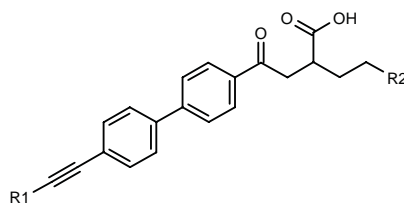
258977

2(*R*)-[2-[4'-(3-Hydroxy-1-propynyl)biphenyl-4-yl]-2-oxoethyl]-5-phenylpentanoic acid

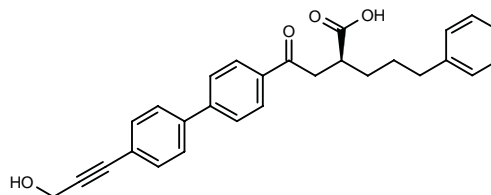


C₂₈-H₂₆-O₄; Mol wt: 426.51

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases (MMPs), particularly MMP-3 (human stromelysin; IC₅₀ = 5 μM), MMP-9 (human recombinant progelatinase B; IC₅₀ = 37 μM) and MMP-2 (human recombinant progelatinase A; IC₅₀ = 1 μM). Also claimed for the treatment of other conditions involving MMPs such as tumor metastasis and osteopenias. Within this series of acetylene-containing compounds, the following are also included:



Compound	R1	R2	Formula
259829	CH ₂ OH	CH ₂ Ph	C ₂₈ H ₂₆ O ₄
259831	CH ₂ OCOEt	CH ₂ Ph	C ₃₁ H ₃₀ O ₆
259832	CH ₂ OMe	CH ₂ Ph	C ₂₉ H ₂₈ O ₄
259833	CH(Pr) ₂	CH ₂ Ph	C ₃₄ H ₃₈ O ₃
259834	CH ₂ OAc	CH ₂ Ph	C ₃₀ H ₂₈ O ₅
259835	CH ₂ CH ₂ OH	CH ₂ Ph	C ₂₉ H ₂₈ O ₄
259836	(CH ₂) ₂ OAc	CH ₂ Ph	C ₃₁ H ₃₀ O ₅
259837	CH ₂ CH ₂ CO ₂ H	CH ₂ Ph	C ₃₀ H ₂₈ O ₅
259838	(CH ₂) ₃ CHO	CH ₂ Ph	C ₃₁ H ₃₀ O ₄
259839	(CH ₂) ₄ OH	CH ₂ Ph	C ₃₁ H ₃₂ O ₄
259840	Ph	CH ₂ Ph	C ₃₃ H ₂₈ O ₃
259842	3-OH-Ph	CH ₂ Ph	C ₃₃ H ₂₈ O ₄
259843	CH ₂ OCH ₂ Ph	1,3-dioxo-2-isoindolyl	C ₃₆ H ₂₉ NO ₆
259844	CH ₂ OH	1,3-dioxo-2-isoindolyl	C ₂₉ H ₂₃ NO ₆



259830: C₂₈-H₂₆-O₄

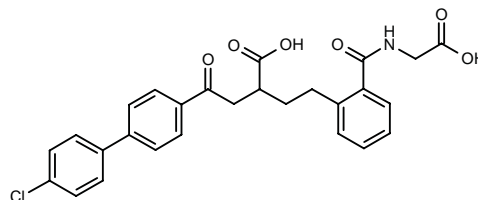
SOURCE – Bayer.

REFERENCES

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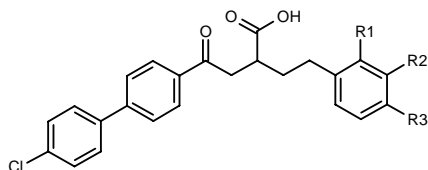
258978

4-(4'-Chlorobiphenyl-4-yl)-2-[2-[2-[*N*-(carboxymethyl)carbamoyl]phenyl]ethyl]-4-oxobutyric acid



C₂₇-H₂₄-Cl-N-O₆; Mol wt: 493.94

ACTION – Antiarthritic agent, an inhibitor of matrix metalloproteinases (MMPs), particularly MMP-3 (human stromelysin; K_i = 259 nM), MMP-9 (human recombinant progelatinase B; K_i = 1590 nM) and MMP-2 (human recombinant progelatinase A; K_i = 96.0 nM). Also claimed for the treatment of other conditions involving MMPs such as tumor metastasis and osteopenias. Within this series of substituted phenethyl compounds, the following are also included:



Compound	R1	R2	R3	Formula
259784	CONH-CH ₂ CO ₂ Et	H	H	C ₂₉ H ₂₈ ClNO ₆
259785	H	CONHCH ₂ CH ₂ Ph	H	C ₃₃ H ₃₀ ClNO ₄
259786	H	H	CONH-CH ₂ CO ₂ H	C ₂₇ H ₂₄ ClNO ₆
259787	H	i-BuCH ₂ NHCO	H	C ₃₀ H ₃₂ ClNO ₄

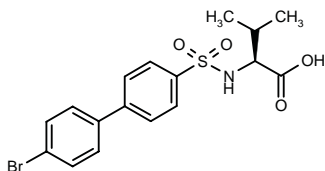
SOURCE – Bayer.

REFERENCES

1. Wolanin, D.J. (Bayer Corp.) *Inhibition of matrix metalloproteinases by subst. phenethyl cpds.* WO 9743247.

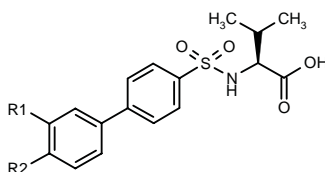
259040

N-(4'-Bromobiphenyl-4-ylsulfonyl)-L-valine



C₁₇-H₁₈-Br-N-O₄-S; Mol wt: 412.30

ACTION – Agent for the treatment of diseases caused by the breakdown of connective tissue such as arthritis, atherosclerosis, restenosis and osteoporosis that inhibits matrix metalloproteinases (MMPs), as demonstrated by its ability to inhibit gelatinase A-catalyzed hydrolysis of thiopeptolide (IC₅₀ = 0.005 μM) and gelatin (IC₅₀ = 0.025 μM), and stromelysin-catalyzed hydrolysis of thiopeptolide (IC₅₀ = 0.012 μM). In addition, the compound was tested for its ability to inhibit full-length collagenase hydrolysis of thiopeptolide (IC₅₀ = 3.24 μM) and full-length gelatinase B hydrolysis of thiopeptolide (IC₅₀ = 8.34 μM). Within this series of biphenylsulfonamides, the following are also included:



Compound	R1	R2	Formula
260226	H	Cl	C ₁₇ H ₁₈ ClNO ₄ S
260227	Br	H	C ₁₇ H ₁₈ BrNO ₄ S

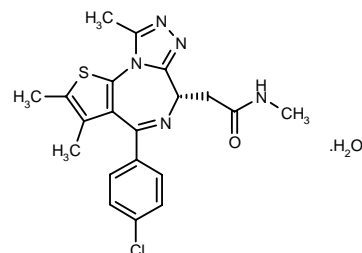
SOURCE – Warner-Lambert.

REFERENCES

1. O'Brien, P.M. and Sliskovic, D.R. (Warner-Lambert Co.) *Biphenylsulfonamide matrix metalloproteinase inhibitors.* WO 9744315.

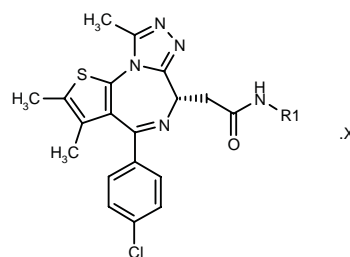
259393

2-[4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*]-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-6(*S*)-yl]-*N*-methylacetamide hydrate



C₂₀-H₂₀-Cl-N₅-O-S.H₂O; Mol wt: 431.94

ACTION – Antiinflammatory and antiallergic agent with cell adhesion-inhibitory activity. *In vitro*, it inhibited CD11b expression in human histiocytic leukemia U937 cells (IC₅₀ = 0.26 μM), as well as VCAM-1 and ELAM-1 expression in human umbilical vein endothelial cells (HUVEC; IC₅₀ = 0.025 and 0.052 μM, respectively). When administered orally to mice, it was found to dose-dependently inhibit oxazolone-induced ear edema, thioglycolate-induced leukocyte infiltration into the peritoneal cavity (0.03-0.3 mg/kg) and lipopolysaccharide (LPS)-induced leukocyte adhesion (0.3-3 mg/kg). In a trinitrobenzenesulfonic acid (TNBS)-induced ulcerative colitis model in the rat, it was found to significantly inhibit the increase in intestinal weight and leukocyte infiltration at 1 mg/kg/day p.o. x 5 days. In addition, it proved effective in a model of glomerulonephritis in mice at 1 mg/kg/day p.o. x 13 days and was found to inhibit ovalbumin-induced eosinophil infiltration into bronchoalveolar lavage (BAL) in guinea pigs at 30 mg/kg p.o. No deaths were observed following p.o. administration of 1000 mg/kg to mice. A representative compound from a series of thienotriazolodiazepine derivatives, wherein the following are also included:

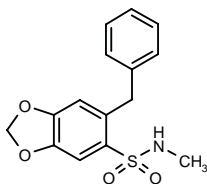


Compound	R1	X	Formula
260007	CH ₂ CH ₂ OH	H ₂ O	C ₂₁ H ₂₂ ClN ₆ O ₂ S.H ₂ O
260008	4-OH-Ph	H ₂ O	C ₂₅ H ₂₂ ClN ₆ O ₂ S.H ₂ O
260009	4-NH ₂ -Ph	H ₂ O	C ₂₅ H ₂₃ ClN ₆ OS.H ₂ O
260010	3-Pyr	HCl	C ₂₄ H ₂₁ ClN ₆ OS.HCl

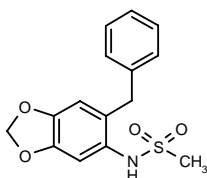
SOURCE – Yoshitomi.

REFERENCES

1. Sueoka, H. et al. (Yoshitomi Pharm. Ind., Ltd.) *Thienotriazolodiazepine cpds. and their pharmaceutical use.* US 5712274.

2597546-Benzyl-*N*-methyl-1,3-benzodioxole-5-sulfonamideC₁₅-H₁₅-N-O₄-S; Mol wt: 305.35

ACTION – Antiinflammatory agent, an analog of the cyclooxygenase type 2 (COX-2) inhibitor flosulide shown to be more potent than indomethacin and nimesulide in the carrageenan-induced pleurisy model in rats (46.0% inhibition at 100 μmol/kg p.o. vs. 31.7 and 29.9% inhibition, respectively, for indomethacin and nimesulide at the same dose). The corresponding retrosulfonamide exhibited a similar profile and was also selected for further studies:

**259755:** C₁₅-H₁₅-N-O₄-S

SOURCE – Univ. Fed. Rio de Janeiro, Rio de Janeiro (BR).

REFERENCES

1. Lages, A.S. et al. *Synthesis and pharmacological evaluation of new flosulide analogues, synthesized from natural safrole*. Bioorg Med Chem Lett 1998, 8(2): 183.

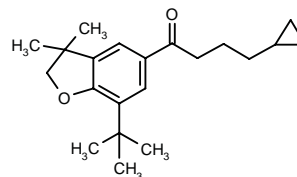
FO-5904**256470**

ACTION – Collagenase inhibitor isolated from *Aspergillus niger* FO-5904 (FERM P-15397), with an IC₅₀ value of 170 μM against human enzyme. Compound also exhibited influenza virus sialidase-inhibitory activity and displayed antiviral activity in influenza virus A/PR/8/34-infected MDCK cells at 140 μM. It is reported to possess good stability and low toxicity. Potentially useful for the treatment of rheumatoid arthritis, inflammation, tumors and influenza virus infections.

SOURCE – Kitasato Inst., Tokyo (JP).

REFERENCES

1. Omura, S. et al. (Kitasato Inst.) *Novel collagenase inhibitory substance FO-5904 and the preparation method*. JP 97241287.

PGV-20229***236184**1-(7-*tert*-Butyl-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-4-cyclopropyl-1-butanoneC₂₁-H₃₀-O₂; Mol wt: 314.47

ACTION – Antiinflammatory and analgesic agent, a dihydrobenzofuran derivative structurally related to the di-*tert*-butylphenol class of nonsteroidal antiinflammatory drugs (NSAIDs), with selectivity for cyclooxygenase type 2 (COX-2; IC₅₀ = 0.22 μM) relative to COX-1 (IC₅₀ = 7 μM) and which also inhibits leukotriene synthesis (IC₅₀ = 8 μM). The compound is orally active in animal models of inflammation and pain and is not associated with gastrointestinal toxicity; it was also able to prevent indomethacin-induced gastric damage in rats, which is suggested to be due to its inhibitory activity against 5-lipoxygenase.

SOURCE – Procter & Gamble.

REFERENCES

1. Scherz, M.W. and Matthews, R.S. (The Procter & Gamble Co.) *Dihydrobenzofuran and related cpds. useful as anti-inflammatory agents*. US 5656661, US 5674891, WO 9603396.

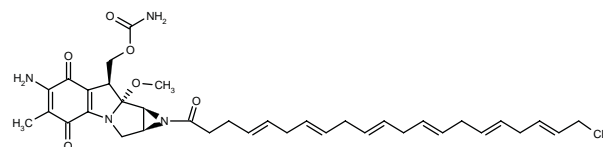
2. Knight, P.M. et al. *Analysis of a novel antiinflammatory agent, 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzo[b]furan-5-yl)-4-cyclopropylbutan-1-one (PGV-20229), in plasma matrices by stable-isotope-dilution gas chromatography mass spectrometry*. J Chromatogr B 1997, 700(1-2): 111.

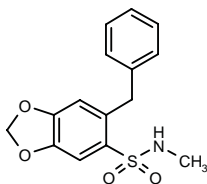
3. Parnham, M.J. *Inflammation: Mechanisms and therapeutics*. Drug News Perspect 1996, 9(10): 631.

*Identified compound **236184** (see **235748**) Drug Data Rep 1996, 18(6): 556.

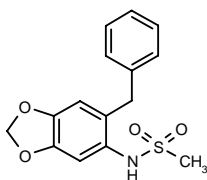
IMMUNOLOGIC DRUGS**257182**

(1*a*S,8*S*,8*a*R,8*b*S)-6-Amino-8-(carbamoylexymethyl)-1-(docosa-4,7,10,13,16,19-hexaenoyl)-8*a*-methoxy-5-methyl-1,1*a*,2,4,7,8,8*a*,8*b*-octahydroazirino[2',3':3,4]-pyrrolo[1,2-*a*]indole-4,7-dione

C₃₇-H₄₈-N₄-O₆; Mol wt: 644.81

2597546-Benzyl-*N*-methyl-1,3-benzodioxole-5-sulfonamideC₁₅-H₁₅-N-O₄-S; Mol wt: 305.35

ACTION – Antiinflammatory agent, an analog of the cyclooxygenase type 2 (COX-2) inhibitor flosulide shown to be more potent than indomethacin and nimesulide in the carrageenan-induced pleurisy model in rats (46.0% inhibition at 100 μmol/kg p.o. vs. 31.7 and 29.9% inhibition, respectively, for indomethacin and nimesulide at the same dose). The corresponding retrosulfonamide exhibited a similar profile and was also selected for further studies:

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SOURCE – Univ. Fed. Rio de Janeiro, Rio de Janeiro (BR).

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1. Lages, A.S. et al. *Synthesis and pharmacological evaluation of new flosulide analogues, synthesized from natural safrole*. Bioorg Med Chem Lett 1998, 8(2): 183.

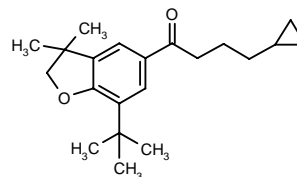
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SOURCE – Kitasato Inst., Tokyo (JP).

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PGV-20229***236184**1-(7-*tert*-Butyl-3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)-4-cyclopropyl-1-butanoneC₂₁-H₃₀-O₂; Mol wt: 314.47

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SOURCE – Procter & Gamble.

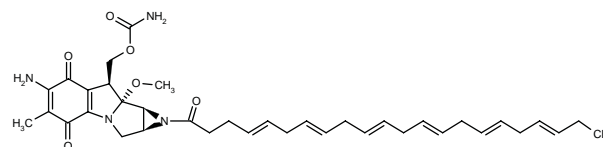
REFERENCES

1. Scherz, M.W. and Matthews, R.S. (The Procter & Gamble Co.) *Dihydrobenzofuran and related cpds. useful as anti-inflammatory agents*. US 5656661, US 5674891, WO 9603396.
2. Knight, P.M. et al. *Analysis of a novel antiinflammatory agent, 1-(7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzo[b]furan-5-yl)-4-cyclopropylbutan-1-one (PGV-20229), in plasma matrices by stable-isotope-dilution gas chromatography mass spectrometry*. J Chromatogr B 1997, 700(1-2): 111.
3. Parnham, M.J. *Inflammation: Mechanisms and therapeutics*. Drug News Perspect 1996, 9(10): 631.

*Identified compound **236184** (see **235748**) Drug Data Rep 1996, 18(6): 556.

IMMUNOLOGIC DRUGS**257182**

(1*a*S,8*S*,8*a*R,8*b*S)-6-Amino-8-(carbamoylexymethyl)-1-(docosa-4,7,10,13,16,19-hexaenoyl)-8*a*-methoxy-5-methyl-1,1*a*,2,4,7,8,8*a*,8*b*-octahydroazirino[2',3':3,4]-pyrrolo[1,2-*a*]indole-4,7-dione

C₃₇-H₄₈-N₄-O₆; Mol wt: 644.81

ACTION – Mitomycin C derivative with excellent inhibitory activity against nonreceptor protein tyrosine kinases believed to be involved in immune diseases and lower activity against other protein kinases such as cAMP-dependent protein kinase, protein kinase C, calmodulin-dependent kinase and epidermal growth factor (EGF) receptor tyrosine kinase. Compound exhibited lower cytotoxicity against murine P388 leukemia compared to mitomycin C (IC_{50} = 21.0 and 1.9 μ g/ml, respectively).

SOURCE – Sagami.

REFERENCES

1. Yazawa, K. et al. (Sagami Chem. Res. Center) *Mitomycin C deriv. and non-receptor tyrosine kinase inhibitor*. JP 97268190, WO 9736904.

260080

Neisseria meningitidis group B vaccine

ACTION – Meningococcal vaccine, particularly for group B serotype meningococci (*Neisseria meningitidis*), that comprises an antigenic peptide ligand which can act as an immunogen capable of eliciting an immune response to produce antibodies against the capsular polysaccharide of group B meningococci, or an antibody that specifically recognizes and binds the synthetic polypeptide of the ligand and the group B meningococcal capsular polysaccharide.

SOURCE – Peptide Therapeutics.

REFERENCES

1. Laing, P. et al. (Peptide Therap., Ltd.) *Meningococcal vaccine*. WO 9746582.

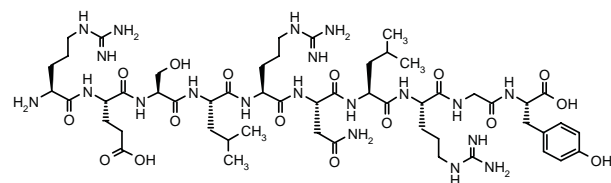
ALLOTRAP-07

259053

Arginyl-glutamyl-seryl-leucyl-arginyl-asparaginyl-leucyl-arginyl-glycyl-tyrosine

B7.75-84

HLA-B7.75-84



C53-H90-N20-O16; Mol wt: 1263.42

ACTION – Synthetic peptide corresponding to residues 75-84 of the α_1 domain of the HLA-B7 molecule with immunosuppressive properties. The peptide inhibits cytotoxic T-cell (CTL) responses against major histocompatibility complex (MHC) class I alloantigens *in vitro* and has proven active, alone and/or in combination with ciclosporin, in prolonging the survival of rat heart allografts. In a Lewis-to-ACI rat heterotopic cardiac allograft model, treatment with peptide plus a subtherapeutic dose of ciclosporin resulted in indefinite survival in 75% of recipients, and long-term donor-specific tolerance was observed in these animals. Treatment with the peptide plus ciclosporin was also synergistic in a Lewis-Fischer 344 rat model of chronic cardiac allograft rejection, and the addition of Allotrap-07 was also able to prevent trans-

plant arteriosclerosis. Slight but significant prolongation of graft survival in a highly immunogenic small bowel transplant model in rats was also observed after treatment with the peptide. It is currently in clinical trials in transplant recipients.

SOURCES – Leland Stanford Junior Univ., Palo Alto, CA (US); SangStat Medical.

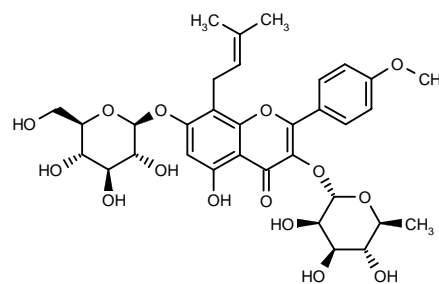
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1. Clayberger, C. et al. (Leland Stanford Junior Univ.) *Immunomodulating dimers*. WO 9744351.
2. Clayberger, C. and Krensky, A.M. (Leland Stanford Junior Univ.) *Immunomodulating cpds. comprising D-isomers of amino acids*. WO 9744052.
3. Clayberger, C.A. and Krensky, A.M. (Leland Stanford Junior Univ.) *Lymphocyte activity regulation by HLA peptides*. WO 9317699.
4. Buelow, R. et al. *Prolongation of skin allograft survival in mice following administration of Allotrap*. Transplantation 1995, 59(4): 455.
5. Cuturi, M.-C. et al. *Prolongation of allogeneic heart graft survival in rats by administration of a peptide (a.a. 75-84) from the alpha1 helix of the first domain of HLA-B7 01*. Transplantation 1995, 59(5): 661.
6. Hanaway, M.J. et al. *Immunosuppressive effects of an HLA class I-derived peptide in a rat cardiac allograft model*. Transplantation 1996, 61(8): 1222.
7. Murphy, B. et al. *Synthetic MHC class I peptide prolongs cardiac survival and attenuates transplant arteriosclerosis in the Lewis Fischer 344 model of chronic allograft rejection*. Transplantation 1997, 64(1): 14.
8. Nisco, S. et al. *Induction of allograft tolerance in rats by an HLA class-I-derived peptide and cyclosporine A1*. J Immunol 1994, 152(8): 3786.
9. Tice, D.G. et al. *Survival of rat small bowel allografts treated with Allotrap 07*. J Surg Res 1997, 72(1): 78.

ICARIIN

260563

3-(6-Deoxy- α -L-mannopyranosyloxy)-7-(β -D-glucopyranosyloxy)-5-hydroxy-2-(4-methoxyphenyl)-8-(3-methyl-2-butenyl)-4H-1-benzopyran-4-one



C33-H40-O15; Mol wt: 676.67

ACTION – Flavanol glycoside isolated from the aerial parts of *Epimedium grandiflorum*, *Epimedium sagittatum*, *Epimedium koreanum*, and the stems and leaves of *Epimedium brevicornum*. The compound has been shown to exert positive effects on the immunological system and on the vascular system. It also exhibits antitumor effects, prevents bone loss and osteoporosis, and has androgen-like properties and antihepatotoxic effects.

SOURCE – Inst. Basic Med. Sci., Shandong Prov. Acad., Jinan (CN).

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1. Ding, Y. et al. *Immunopharmacologic effects of Epimedium polysaccharide and ICA on mouse thymus*. Chin Pharmacol Bull 1993, 9(5): 342.

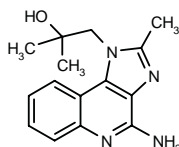
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3. Guo, S.-G. et al. *Research on the relationship between quantitative distribution of 3H-ICA and the meridian affinity*. J Beijing Univ TCM 1997, 20(1): 40.
4. Lee, M.-K. et al. *Antihepatotoxic activity of ICA, a major constituent of Epimedium koreanum*. Planta Med 1995, 61(6): 532.
5. Li, Q.-N. et al. *Skeletal effects of Epimedium in orchietomized rats*. Chin Trad Herb Drugs 1993, 24(12): 637.
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16. Wang, M. et al. *Effects of Epimedium ICA on rabbit and dog vascular smooth muscle*. J Shenyang Coll Pharm 1993, 10(3): 185.
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18. Yang, C.-X. et al. *Chemical constituents of xinyeyinyanghuo (E. brevicorum)*. Chin Trad Herb Drugs 1980, 11(10): 444.
19. Zhao, Y. et al. *Studies on the immuno modulatory action of ICA*. Chin Trad Herb Drugs 1996, 27(11): 669.
20. Zhao, Y. et al. *Study of synergistic effects of ICA on inducing IL-2,3,6*. Chin J Immun 1996, 12(1): 43.
21. Zhao, Y. et al. *Effects of ICA on the proliferation and differentiation of HL-60 cells*. Chin Pharmacol Bull 1996, 12(1): 52.
22. Zhao, Y. et al. *Effects of icariin on the differentiation of HL-60 cells*. Chin J Oncol 1997, 19(1): 53.
23. Zhao, Y. et al. *Effects of icariin on several oncocytes*. Shanghai J Immun 1995, 15(3): 167.

MONOGRAPH – Jiyun, L. et al. *Icariin*. Drugs Fut 1998, 23(2): 142.

S-27609

209724

1-(4-Amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)-2-methyl-2-propanol



C15-H18-N4-O; Mol wt: 270.33

ACTION – Immunomodulator, an analog of imiquimod with potent antitumor and antiviral effects mediated mainly by the induction of cytokines including interferon alfa, tumor necrosis factor (TNF- α), IL-1 α , IL-1 β , IL-1 receptor antagonist (IL-1RA), IL-6 and IL-8; it is more potent than imiquimod as a cytokine inducer.

SOURCE – 3M Pharm.

REFERENCES

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10. Wagner, T.L. et al. *Induction of cytokines in cynomolgus monkeys by the immune response modifiers, imiquimod, S-27609 and S-28463*. Cytokine 1997, 9(11): 837.

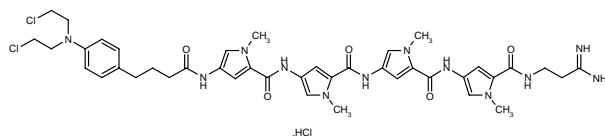
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

MEN-10710

222495

3-[4-[4-[4-[4-[4-[4-[N,N-Bis(2-chloroethyl)amino]-phenyl]butyramido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]propionamidide hydrochloride



C41-H50-Cl2-N12-O5.HCl; Mol wt: 898.29

2. Guan, L.-X. et al. *Vasodilating mechanism of Epimedium icariine*. Chin Pharmacol Bull 1996, 12(4): 320.

3. Guo, S.-G. et al. *Research on the relationship between quantitative distribution of 3H-ICA and the meridian affinity*. J Beijing Univ TCM 1997, 20(1): 40.

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5. Li, Q.-N. et al. *Skeletal effects of Epimedium in orchietomized rats*. Chin Trad Herb Drugs 1993, 24(12): 637.

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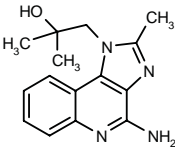
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MONOGRAPH – Jiyun, L. et al. *Icariin*. Drugs Fut 1998, 23(2): 142.

S-27609

209724

1-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methyl-2-propanol



C15-H18-N4-O; Mol wt: 270.33

ACTION – Immunomodulator, an analog of imiquimod with potent antitumor and antiviral effects mediated mainly by the induction of cytokines including interferon alfa, tumor necrosis factor (TNF-α), IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-6 and IL-8; it is more potent than imiquimod as a cytokine inducer.

SOURCE – 3M Pharm.

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10. Wagner, T.L. et al. *Induction of cytokines in cynomolgus monkeys by the immune response modifiers, imiquimod, S-27609 and S-28463*. Cytokine 1997, 9(11): 837.

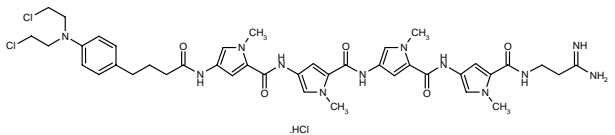
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

MEN-10710

222495

3-[4-[4-[4-[4-[4-[4-[*N,N*-Bis(2-chloroethyl)amino]phenyl]butyramido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]propionamidine hydrochloride



C41-H50-Cl2-N12-O5.HCl; Mol wt: 898.29

ACTION – Antineoplastic agent belonging to a novel class of distamycin-related alkylating agents with an improved ability to strongly bind DNA. MEN-10710 showed enhanced cytotoxic activity when compared with other alkylating agents (L-PAM and tallimustine) both in sensitive and resistant murine ($IC_{50} = 0.014 \pm 0.004$ and $0.018 \pm 0.011 \mu M$, respectively, in sensitive and L-PAM-resistant L1210 murine leukemia cells) and human tumor cell lines ($IC_{50} = 0.059 \pm 0.02$ and $0.248 \pm 0.12 \mu M$, respectively, in sensitive and doxorubicin-resistant human colon carcinoma LoVo cells; $IC_{50} = 0.016 \pm 0.01$ and $0.079 \pm 0.02 \mu M$, respectively, in sensitive and doxorubicin-resistant human mammary carcinoma MCF-7 cells). Likewise, the compound demonstrated enhanced *in vivo* antitumor activity against human tumor xenografts (human epidermoid A431, human non-small cell lung H460 and cisplatin-resistant human ovarian A2780/DDP carcinomas) in mice. It exhibited less inhibition of GM-CSF-dependent murine bone marrow colony formation ($IC_{50} = 7 \pm 2$ nM) compared to tallimustine ($IC_{50} = 0.6 \pm 0.3$ nM) and a better therapeutic index (IC_{50} bone marrow/ IC_{50} tumor cells = 0.23 vs 0.002 for tallimustine).

SOURCE – Menarini.

REFERENCES

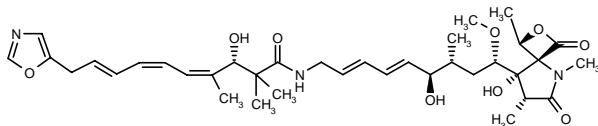
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2. Bigioni, M. et al. *Biological profile of MEN 10710, a distamycin-A derivative possessing antitumor activity and peculiar mode of DNA interaction*. Proc Amer Assoc Cancer Res 1995, 36: Abst 2233.
3. Bigioni, M. et al. *Cytotoxic and antitumor activity of MEN 10710, a novel alkylating derivative of distamycin*. Anti-Cancer Drugs 1997, 8(9): 845.
4. Ciucci, A. et al. *Backbone and benzoyl mustard carrying moiety modifies DNA interactions of distamycin analogs*. Nucleic Acids Res 1996, 24(2): 311.

ANTIBIOTICS AND ALKALOIDS

16-METHYLOXAZOLOMYCIN

258362

[4*S*-[4 α ,7 β ,8 β ,8[1(3*S**,4*Z*,6*Z*,8*E*),2*E*,4*E*,6*S**,7*S**,9*R**]]]-3-Hydroxy-*N*-[6-hydroxy-9-(8-hydroxy-3,5,7-trimethyl-1,6-dioxo-2-oxa-5-azaspiro[3.4]oct-8-yl)-9-methoxy-7-methyl-2,4-nonadienyl]-2,2,4-trimethyl-10-(5-oxazolyl)-4,6,8-decatrienamide



C36-H51-N3-O9; Mol wt: 669.81

Pale yellow amorphous powder, $[\alpha]_D^{23} +3.6^\circ$ (c 0.52, MeOH).

ACTION – Antimicrobial, antialgal and cytotoxic agent produced by a *Streptomyces* sp., exhibiting MIC values of 5.0 and 10.0 $\mu g/ml$, respectively, against *Bacillus subtilis* 1069 and *Chlorella vulgaris* IFO 15941, as well as cytotoxic activity against murine P388 leukemia and human lung adenocarcinoma A-549 cells ($IC_{50} = 0.23$ and 4.6 $\mu g/ml$, respectively).

SOURCE – Korea Ginseng Tobacco Res. Inst., Taejon (KR).

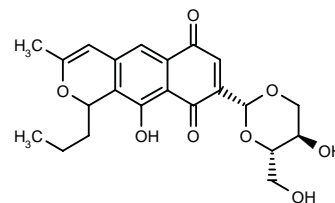
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BE-41956A

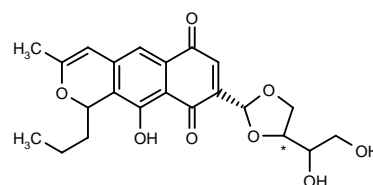
256449

10-Hydroxy-8-[5(*R*)-hydroxy-4(*S*)-(hydroxymethyl)-1,3-dioxan-2(*R*)-yl]-3-methyl-1-propyl-6,9-dihydro-1*H*-naphtho[2,3-*c*]pyran-6,9-dione



C22-H24-O8; Mol wt: 416.43

ACTION – Antineoplastic agent isolated from *Streptomyces* sp. A41956 (FERM P-14445), with potent *in vitro* cytotoxicity against murine leukemia P388, murine colon 26, human colon DLD-1, human lung PC-13 and human stomach MKN-45 cancer cell lines ($IC_{50} = 0.59$, 0.86, 0.43, 0.64 and 1.40 $\mu g/ml$, respectively). Other related compounds are:



Compound	*Isomer	Formula
BE-415956B [260367]	R	C ₂₂ H ₂₄ O ₈
BE-415956C [260368]	S	C ₂₂ H ₂₄ O ₈

SOURCE – Banyu.

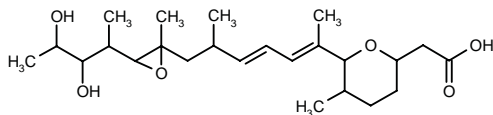
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GEX1Q5

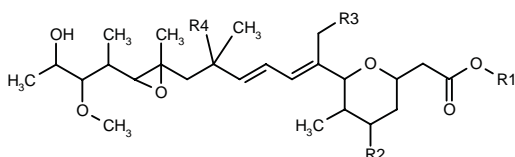
256444

2-[6-[7,8-Epoxy-10,11-dihydroxy-1,5,7,9-tetramethyl-1(*E*), 3(*E*)-dodecadienyl]-5-methyltetrahydropyran-2-yl]acetic acid



C24-H40-O6; Mol wt: 424.58

ACTION – Antineoplastic agent isolated from *Streptomyces* sp. GEX1 (FERM BP-5347), with potent *in vitro* antiproliferative activity against human epidermoid carcinoma A431 cells ($IC_{50} = 0.0053 \mu\text{g/ml}$). Other related compounds include the following:



Compound	R1	R2	R3	R4	Formula
GEX1Q1 [260391]	H	OH	H	H	C ₂₅ H ₄₂ O ₇
GEX1Q2 [260392]	H	H	H	OH	C ₂₅ H ₄₂ O ₇
GEX1Q3 [260393]	6-CO ₂ H- -3,4,5-(OH)3-2-THP	H	H	H	C ₃₁ H ₅₀ O ₁₂
GEX1Q4 [260394]	H	H	OH	H	C ₂₅ H ₄₂ O ₇

SOURCE – Kyowa Hakko.

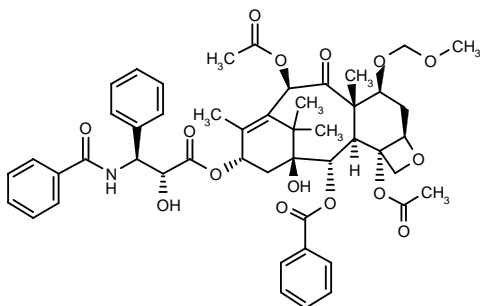
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ANTIMITOTIC DRUGS

258961

[2a*R*]-[2a α ,4 β ,4a β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12a α ,12b α]-6,12b-Diacetoxy-9-(3-benzamido-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-11-hydroxy-4-(methoxymethoxy)-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C49-H55-N-O15; Mol wt: 897.97

ACTION – Antineoplastic agent, a paclitaxel analog proven active *in vivo* in prolonging the survival of mice bearing M109 lung carcinoma (T/C = 192% at 50 mg/kg i.p. on days 5 and 8 after tumor implantation).

SOURCE – Bristol-Myers Squibb.

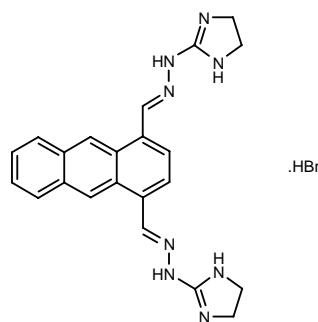
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1. Wittman, M.D. (Bristol-Myers Squibb Co.) *7-O-Methoxymethyl paclitaxel*. WO 9742948.

DNA-INTERCALATING DRUGS

259756

1,4-Anthracenedicarboxaldehyde bis[(4,5-dihydro-1*H*-imidazol-2-yl)hydrazone] hydrobromide



C22-H22-N8.HBr; Mol wt: 479.38

ACTION – Cytotoxic agent, a bisantrene analog that suppresses topoisomerase II-mediated DNA damage; it shows *in vitro* cytotoxicity in human ovarian cancer A2780 ($IC_{50} = 4.8 \mu\text{M}$) and human promyelocytic leukemia HL60 cells ($IC_{50} = 11.2 \mu\text{M}$). It is thus able to induce cytotoxic effects through a mechanism of action distinct from that displayed by bisantrene and may represent a novel lead for the development of anticancer drugs with novel activity profiles.

SOURCE – Boehringer Mannheim.

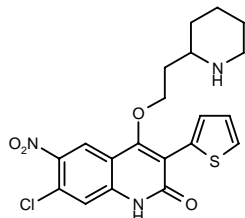
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HORMONAL AGENTS

259027

7-Chloro-6-nitro-4-[2-(2-piperidyl)ethoxy]-3-(2-thienyl)-quinolin-2(1*H*)-one



C20-H20-Cl-N3-O4-S; Mol wt: 433.91

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist for the treatment of sex hormone-dependent cancers, benign prostatic hypertrophy, uterine myoma, endometriosis, polycystic ovarian disease, uterine fibroids, premenstrual syndrome, lupus erythematosus, hirsutism, irritable bowel syndrome and sleep disorders, as well as for use as a contraceptive and as an adjunct to growth hormone therapy in growth hormone-deficient children.

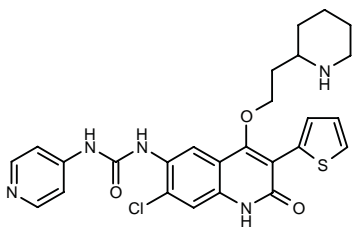
SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9744037.

259030

N-[7-Chloro-2-oxo-4-[2-(2-piperidyl)ethoxy]-3-(2-thienyl)-1,2-dihydroquinolin-6-yl]-*N'*-(4-pyridyl)urea



C26-H26-Cl-N5-O3-S; Mol wt: 524.04

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist for the treatment of sex hormone-dependent cancers, benign prostatic hypertrophy, uterine myoma, endometriosis, polycystic ovarian disease, uterine fibroids, premenstrual syndrome, lupus erythematosus, hirsutism, irritable bowel syndrome and sleep disorders, as well as for use as a contraceptive and as an adjunct to growth hormone therapy in growth hormone-deficient children.

SOURCE – Merck & Co.

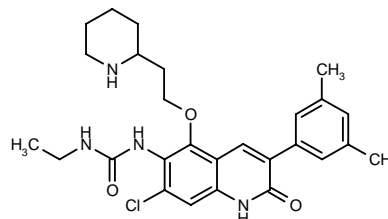
REFERENCES

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259041

7-Chloro-3-(3,5-dimethylphenyl)-6-(3-ethylureido)-5-[2-(2-piperidyl)ethoxy]quinolin-2(1*H*)-one

N-[7-Chloro-3-(3,5-dimethylphenyl)-2-oxo-5-[2-(2-piperidyl)ethoxy]-1,2-dihydroquinolin-6-yl]-*N'*-ethylurea



C27-H33-Cl-N4-O3; Mol wt: 497.04

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist claimed for use in the treatment of a variety of sex hormone-related conditions including prostate, uterine and breast cancer, endometriosis, polycystic ovarian disease and short stature or growth hormone deficiency, and for preventing pregnancy.

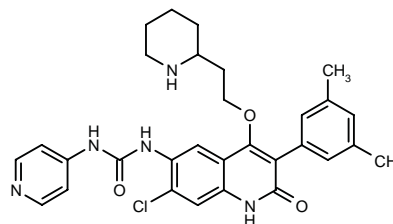
SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9744321.

259050

N-[7-Chloro-3-(3,5-dimethylphenyl)-2-oxo-4-[2-(2-piperidyl)ethoxy]-1,2-dihydroquinolin-6-yl]-*N'*-(4-pyridyl)urea



C30-H32-Cl-N5-O3; Mol wt: 546.07

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist for the treatment of sex hormone-dependent cancers, benign prostatic hypertrophy, uterine myoma, endometriosis, polycystic ovarian disease, uterine fibroids, premenstrual syndrome, lupus erythematosus, hirsutism, irritable bowel syndrome and sleep disorders, as well as for use as a contraceptive and as an adjunct to growth hormone therapy in growth hormone-deficient children.

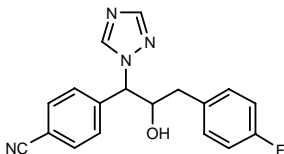
SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 9744339.

MPV-2213ad***213033**

4-[3-(4-Fluorophenyl)-2-hydroxy-1-(1,2,4-triazol-1-yl)-propyl]benzonitrile



C18-H15-F-N4-O; Mol wt: 322.34

ACTION – Orally active, nonsteroidal, competitive aromatase inhibitor with high selectivity for human aromatase *in vitro* ($IC_{50} = 0.18-0.47 \mu M$ in human placental microsomes), and with no significant effects on desmolase or cytochrome P-450 enzymes. MPV-2213ad was shown in phase I clinical trials in healthy male subjects to be a potent, specific and well-tolerated inhibitor of the enzyme, dose-dependently (0.3-300 mg p.o.) reducing serum estradiol levels; levels were decreased 83% from baseline after the dose of 300 mg.

SOURCE – Orion.**REFERENCES**

1. Karjalainen, A.J. et al. (Orion-Yhtymä Oy) *Cyanobenzyl heterocyclic aromatase-inhibiting cpds.* GB 2273704, JP 96504424, US 5703109, WO 9413645.

2. Ahokoski, O. et al. *Hormonal effects of MPV-2213ad, a new selective aromatase inhibitor, in healthy male subjects. A phase I study.* Brit J Clin Pharmacol 1998, 45(2): 141.

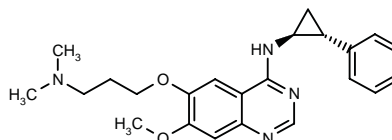
*Identified compound **213033** (see **211672**) Drug Data Rep 1994, 16(11): 1051.

CANCER IMMUNOTHERAPY**MAb 3-8D6****256215**

ACTION – Antibody against human ErbB3 protein with the ability to reduce heregulin-induced formation of an ErbB2–ErbB3 protein complex, and/or the ability to increase the binding affinity of heregulin for ErbB3 protein, or to reduce heregulin-induced ErbB2 activation in a cell expressing ErbB2 and ErbB3. Potentially useful in the treatment of benign and malignant tumors, leukemias and lymphoid malignancies.

SOURCE – Genentech.**REFERENCES**

1. Akita, R. and Sliwkowski, M. (Genentech, Inc.) *ErbB3 antibodies.* WO 9735885.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS**256884***trans*-6-[3-(*N,N*-Dimethylamino)propoxy]-7-methoxy-4-(2-phenylcyclopropylamino)quinazoline*trans*-*N*-[6-[3-(*N,N*-Dimethylamino)propoxy-7-methoxy-quinazolin-4-yl]-*N*-(2-phenylcyclopropyl)amine

C23-H28-N4-O2; Mol wt: 392.50

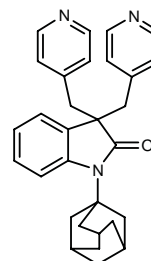
ACTION – Antineoplastic agent, a potent inhibitor of tyrosine kinase activity associated with the epidermal growth factor (EGF) receptor ($IC_{50} = 0.027 \mu M$ for enzyme from vulval squamous carcinoma A431 cells) proven to inhibit EGF-stimulated proliferation of KB cells in cell culture ($IC_{50} = 0.31 \mu M$). It also exhibited significant activity *in vivo* against tumor growth in a tumor xenograft model in nude mice (36% inhibition of vulval carcinoma A431 growth at 50 mg/kg/day p.o. X 21 days).

SOURCE – Zeneca.**REFERENCES**

1. Gibson, K.H. et al. *Epidermal growth factor receptor tyrosine kinase: Structure-activity relationships and antitumour activity of novel quinazolines.* Bioorg Med Chem Lett 1997, 7(21): 2723.

258714

1-(1-Adamanyl)-3,3-bis(4-pyridylmethyl)indolin-2-one



C30-H31-N3-O; Mol wt: 449.59

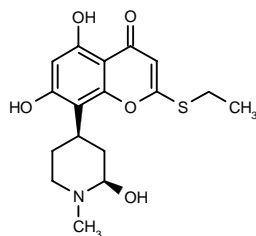
ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase. A specifically claimed compound within a series of adamantyl substituted oxindoles.

SOURCE – Pfizer.**REFERENCES**

1. Lyssikatos, J.P. and Volkmann, R.A. (Pfizer, Inc.) *Adamantyl subst. oxindoles as pharmaceutical agents.* EP 810223.

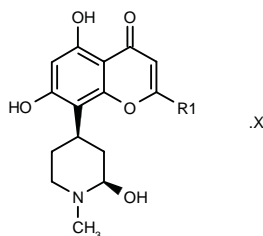
258962

(±)-*cis*-2-(Ethylsulfanyl)-5,7-dihydroxy-8-(2-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one



C17-H21-N-O5-S; Mol wt: 351.42

ACTION – Agent for the treatment of cancer and other proliferative diseases, inflammation and arthritis, an inhibitor of protein kinases such as the cyclin-dependent kinases (cdk), and other kinases including protein kinase C. Within this series of 2-thio- or 2-oxo flavopiridol analogs, the following are also included:



Compound	R1	X	Formula
259338	SPh		C ₂₁ H ₂₁ NO ₅ S
259339	SBu		C ₁₈ H ₂₅ NO ₅ S
259340	2-Cl-PhS		C ₂₁ H ₂₀ ClNO ₅ S
259341	2-Cl-PhO		C ₂₁ H ₂₀ ClNO ₆
259342	SCH ₂ CH ₂ NHAc	CF ₃ CO ₂ H	C ₁₉ H ₂₄ N ₂ O ₆ S.C ₂ HF ₃ O ₂
259343	SCH ₂ CH ₂ OH	CF ₃ CO ₂ H	C ₁₇ H ₂₁ NO ₆ S.C ₂ HF ₃ O ₂

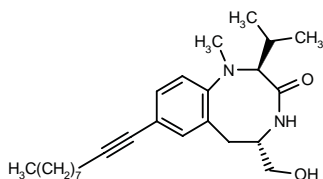
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Kim, K.S. (Bristol-Myers Squibb Co.) 2-Thio or 2-oxo flavopiridol analogs. WO 9742949.

258986

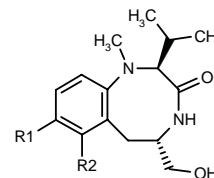
(2*S*,5*S*)-5-(Hydroxymethyl)-2-isopropyl-1-methyl-8-(1-decynyl)-1,2,3,4,5,6-hexahydro-1,4-benzodiazocin-3-one



C25-H38-N2-O2; Mol wt: 398.59

ACTION – Antineoplastic agent, a protein kinase C (PKC) modulator with higher affinity for the α and β isozymes compared to γ, δ and ε isozymes, showing approximately a 10-fold difference in affinity between PKCα and ε. Antiproliferative activity was determined against human breast carcinoma MCF-7 and MDA-MB-231 cell lines (IC₅₀ = 20 and 30 μM, respectively), and it was found to prefer-

entially downregulate PKCβ in both cell lines. In mice bearing human breast carcinoma MDA-MB-231 xenografts, it produced 65% inhibition of tumor growth at a dose of 16 mg/kg/day i.p., with no evidence of toxicity. Other specifically claimed 8-hydrocarbyl substituted benzodiazocine derivatives include the following:



Compound	R1	R2	Formula
259336	C10H21	H	C ₂₅ H ₄₂ N ₂ O ₂
259337	C8H17-ethynylene	OMe	C ₂₆ H ₄₀ N ₂ O ₃

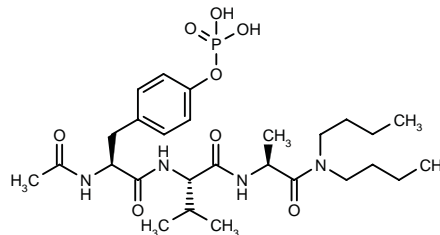
SOURCE – Georgetown Univ., Washington, D.C. (US).

REFERENCES

1. Kozikowski, A.P. and Ma, D. (Georgetown Univ.) 8-Hydrocarbyl subst. benzodiazocine derivs., their preparation and their use as protein kinase C (PKC) modulators. WO 9743268.

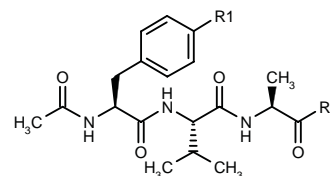
259008

N-Acetyl-4-*O*-phosphono-L-tyrosyl-L-valyl-L-alanine dibutylamide



C27-H45-N4-O8-P; Mol wt: 584.65

ACTION – Agent for the treatment of cancer, restenosis, arthritis, atherosclerosis, psoriasis and neointimal hyperplasia that acts by inhibiting the association of platelet-derived growth factor (PDGF) receptor and phosphatidylinositol 3-kinase, as demonstrated in a binding assay using rat aortic smooth muscle cells (IC₅₀ = 37.5 μM) and by measuring the inhibition of binding of [³⁵S]-p85SH2 fusion proteins to the phosphorylated PDGF-β receptor tyrosine kinase (IC₅₀ = 1.6 0.32 μM). Within this series of specifically claimed compounds, the following are also included:



Compound	R1	R2	Formula
260358	CF ₂ PO(OEt) ₂	OH	C ₂₄ H ₃₆ F ₂ N ₃ O ₈ P
260359	CF ₂ PO(OEt) ₂	N(C5H11) ₂	C ₃₄ H ₅₇ F ₂ N ₄ O ₇ P
260360	CF ₂ PO(OH) ₂	N(C8H17) ₂	C ₃₆ H ₆₁ F ₂ N ₄ O ₇ P
260361	OCH ₂ Ph	OH	C ₂₆ H ₃₃ N ₃ O ₆
260362	OPO ₃ H ₂	N(C5H11) ₂	C ₂₉ H ₄₉ N ₄ O ₈ P
260363	OPO ₃ H ₂	N(C8H17) ₂	C ₃₅ H ₆₁ N ₄ O ₈ P

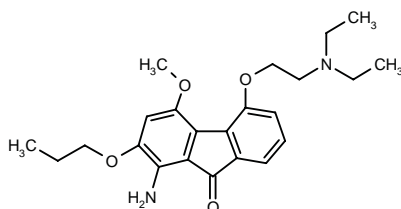
SOURCE – Warner-Lambert.

REFERENCES

1. Cody, W.L. et al. (Warner-Lambert Co.) *Cpds. inhibiting the association of the PDGF receptor and phosphatidylinositol 3-kinase and their use*. WO 9743307.

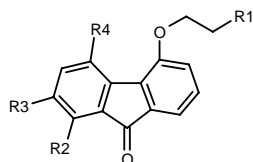
259891

1-Amino-5-[2-(diethylamino)ethoxy]-4-methoxy-2-propoxy-9-fluorenone



C23-H30-N2-O4; Mol wt: 398.50

ACTION – Protein kinase C (PKC) inhibitor (IC_{50} = 0.079 μ M against rat brain enzyme), potentially useful for the treatment of cancer, hypertension, ischemia, atherosclerosis, inflammatory disorders such as transplant rejection, psoriasis, gouty arthritis and lung fibrosis, and for inhibiting platelet aggregation and alveolar macrophage activation. Other compounds from this series of specifically claimed alkyloxyamino substituted fluorenones include the following:



Compound	R1	R2	R3	R4	Formula
260462	N(Et)2	NH2	OMe	OMe	C ₂₁ H ₂₆ N ₂ O ₄
260463	1-pyrrolidinyl	H	OPr	OMe	C ₂₃ H ₂₇ NO ₄
260464	N(Et)2	H	H	OMe	C ₂₀ H ₂₃ NO ₃
260465	N(Et)2	H	OPr	OMe	C ₂₃ H ₂₉ NO ₄
260466	N(Et)2	H	OMe	OMe	C ₂₁ H ₂₅ NO ₄
260467	N(Et)2	H	OCH2CH2N(Et)2	OMe	C ₂₈ H ₃₆ N ₂ O ₄
260468	4-morpholinyl	NH2	OPr	OMe	C ₂₃ H ₂₈ N ₂ O ₅
260469	N(Et)2	H	OMe	H	C ₂₀ H ₂₃ NO ₃
260470	N(Et)2	H	OPr	H	C ₂₂ H ₂₇ NO ₃

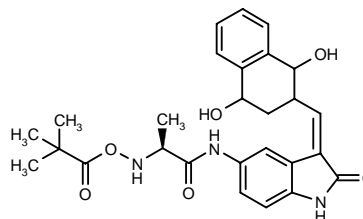
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Jones, W.D. et al. (Hoechst Marion Roussel, Inc.) *Alkyloxyamino substd. fluorenones and their use as protein kinase C inhibitors*. WO 9745397.

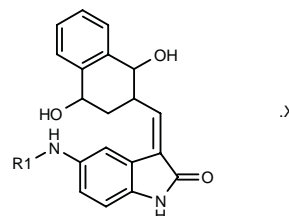
259897

N-tert-Butoxycarbonyl-L-alanine 3-(1,4-dihydroxy-1,2,3,4-tetrahydronaphthalen-2-ylmethylene)-2-oxindolin-5-ylamide



C27-H31-N3-O6; Mol wt: 493.56

ACTION – Antineoplastic agent with improved bioavailability and water solubility over related compounds, a potent inhibitor of tyrosine kinases such as p45 v-abl kinase isolated from Abelson murine leukemia virus (IC_{50} = 1.56 μ M). *In vitro*, it inhibited the growth of human myelogenous leukemia K562 cells with an IC_{50} value of 5.86 μ M. Also claimed for inhibiting the development of atheromatous plaque, for the treatment of Alzheimer's disease and as an immunomodulator. Other compounds from this series of tetralylmethylene-2-oxindole derivatives include the following:



Compound	R1	X	Formula
260559	H-Gln-		C ₂₄ H ₂₆ N ₄ O ₅
260560	H-Ala-		C ₂₂ H ₂₃ N ₃ O ₄
260561	H-Ala-Ala-	CF3CO2H	C ₂₈ H ₂₈ N ₄ O ₅ ·C ₂ HF ₃ O ₂

SOURCE – Pharmacia & Upjohn.

REFERENCES

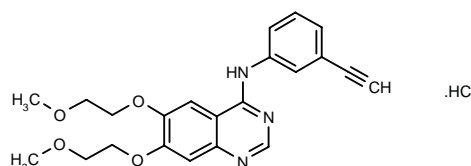
1. Battistini, C. et al. (Pharmacia & Upjohn SpA) *Substd. tetralylmethylene-oxindole analogues as tyrosine kinase inhibitors*. WO 9745409.

CP-358774

250837

4-(3-Ethynylphenylamino)-6,7-bis(2-methoxyethoxy)-quinazoline hydrochloride

N-[6,7-Bis(2-methoxyethoxy)quinazolin-4-yl]-*N*-(3-ethynylphenyl)amine hydrochloride



C22-H23-N3-O4.HCl; Mol wt: 429.90

ACTION – Antineoplastic agent, a potent and selective inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase ($IC_{50} = 2$ nM, $K_i = 2.7$ nM using human enzyme), with over 1000-fold selectivity versus other tyrosine kinases; it inhibited EGF receptor autophosphorylation in human breast cancer MDA-MB-468 cells and human head and neck tumor HN5 cells with an IC_{50} of 20 nM. The compound inhibited the proliferation of human colon tumor DiFi cells with an IC_{50} of 100 nM and completely blocked HN5 cell proliferation at 250 nM; its antiproliferative effects appeared to involve both cell cycle block and the induction of apoptosis. *In vivo*, it inhibited EGF receptor autophosphorylation in liver and HN5 tumors in athymic mice, with complete inhibition at 100 mg/kg i.p., a dose shown to be nontoxic when given daily for 5 days. CP-358774 was also shown to inhibit HN5 xenografts in athymic mice, with an ED_{50} of 10 mg/kg/day x 5 p.o. Currently in phase I clinical trials in cancer patients.

SOURCES – OSI Pharm. (formerly Oncogene Science); Pfizer.

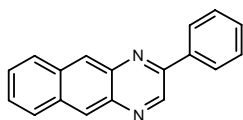
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1. Schnur, R.C. and Arnold, L.D. (Pfizer, Inc.) *Quinazoline derivs.* EP 817775, WO 9630347.
2. Barbacci, E.G. et al. *Induction of cell cycle arrest by inhibitors of epidermal growth factor receptor (EGFR) kinase activity.* Proc Amer Assoc Cancer Res 1997, 38: Abst 3143.
3. Iwata, K. et al. *CP-358,774: A selective EGFR kinase inhibitor with potent antiproliferative activity against HN5 head and neck tumor cells.* Proc Amer Assoc Cancer Res 1997, 38: Abst 4248.
4. Moyer, J.D. et al. *Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase.* Cancer Res 1997, 57(21): 4838.
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6. Potchoiba, M.J. et al. *Tissue distribution of CP-358,774, a selective and potent EGF receptor tyrosine kinase inhibitor in HN5 tumor-bearing, athymic nu/nu (nude) mice.* Proc Amer Assoc Cancer Res 1997, 38: Abst 3139.
7. Smolarek, T.A. et al. *Pharmacokinetics and metabolism of CP-358,774, a potent and selective EGF receptor tyrosine kinase inhibitor.* Proc Amer Assoc Cancer Res 1997, 38: Abst 4010.
8. Updyke, L. et al. *Pre-clinical safety assessment of CP-358,774, an epidermal growth factor receptor tyrosine kinase inhibitor.* Proc Amer Assoc Cancer Res 1997, 38: Abst 3140.
9. *Pfizer enters phase I trials with CP-358774.* Prous Science Daily Essentials August 20, 1997.

ANTIANGIOGENIC AGENTS

259397

2-Phenylbenzo[g]quinoxaline



C18-H12-N2; Mol wt: 256.31

ACTION – Antiangiogenic and antimetastatic agent that acts by modulating KDR/FLK-1, a tyrosine kinase receptor expressed in endothelial cells that is a receptor for vascular endothelial growth factor (VEGF). Compound inhibited FLK-1 receptor protein tyrosine kinase activity in FLK-1/NIH3T3 cells with an IC_{50} value of 4.4 μ M. *In vivo*, it produced 41% inhibition of tumor growth in human lung Calu-6 tumor-bearing mice at 20 mg/kg/day.

SOURCES – Sugen; Yissum.

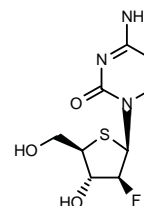
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1. App, H. et al. (Yissum Develop. Res. Co.; Sugen) *Cpds. for the treatment of disorders related to vasculogenesis and/or angiogenesis.* US 5712395.

MISCELLANEOUS ANTINEOPLASTIC AGENTS

257221

1-(2-Deoxy-2-fluoro-4-thia- β -D-arabinofuranosyl)cytosine



C9-H12-F-N3-O3-S; Mol wt: 261.27

ACTION – Antineoplastic agent active *in vitro* against human leukemia CCRF-HSB-2, human nasopharyngeal cancer KB cells and human gastric cancer MKN-45 and MKN-28 cells ($IC_{50} = 0.051, 0.015, 2.1$ and 0.027 μ g/ml, respectively). *In vivo*, it showed potent antitumor activity in mice bearing murine sarcoma S-180 (T/C = 27% at 10 mg/kg/day i.v. x 10 days) and it completely inhibited the growth of human colon SW-48 tumors in mice at 20 mg/kg/day i.v. or p.o. x 10 days.

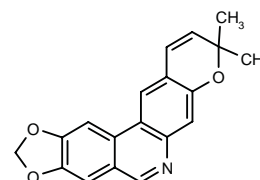
SOURCE – Yamasa.

REFERENCES

1. Yoshimura, Y. et al. (Yamasa Corp.) *1-(2-Deoxy-2-fluoro-4-thio-beta-D-arabinofuranosyl)cytosines.* WO 9738001.

259714

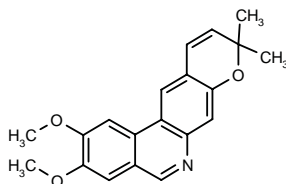
9,9-Dimethyl-2,3-methylenedioxy-9H-pyrano[3,2-b]-phenanthridine



C19-H15-N-O3; Mol wt: 305.33

Amorphous solid.

ACTION – Cytotoxic agent, as shown in *in vitro* assays using both murine leukemia L1210 and human colon carcinoma HT29 cell lines. This compound significantly increased the number of cells in the G2+M phases, which suggests that its cytotoxicity is due to an interaction with DNA. Another promising compound from this series of 9,9-dimethyl-9H-pyrano[3,2-*b*]phenanthridines is:



259640: C20-H19-N-O3

SOURCES – CNRS (Centre Natl. Rech. Sci.); Servier.

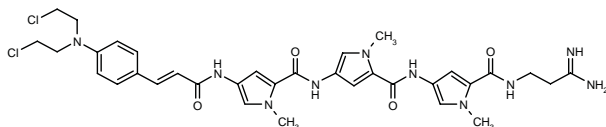
REFERENCES

1. Razafimbelo, J. et al. *Synthesis and cytotoxic activity of pyranophenanthridine analogues of fagaronine and acronycine*. Chem Pharm Bull 1998, 46(1): 34.

FCE-29381

258982

3-[4-[4-[4-[4-[Bis(2-chloroethyl)amino]cinnamoylamino]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]propionamide



C34-H40-Cl2-N10-O4; Mol wt: 723.66

ACTION – Antineoplastic and antiviral agent giving an IC₅₀ value of 7.3 ng/ml when tested for *in vitro* cytotoxicity against murine L1210 leukemia cells. *In vivo*, it prolonged survival time of mice bearing murine L1210 leukemia (T/C x 100 = 267% at 6.25 mg/kg i.v. on day 1 after tumor cell inoculation), no mice dying due to toxicity. A representative compound within a series of specifically claimed distamycin derivatives.

SOURCE – Pharmacia & Upjohn.

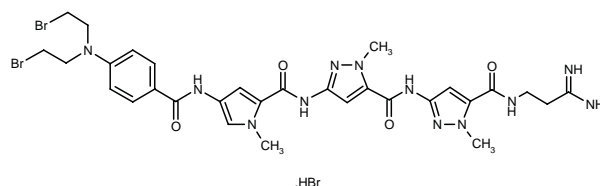
REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Distamycin derivs., process for preparing them, and their use as antitumor and antiviral agents*. WO 9743258.

PNU-157977

259853

3-[3-[3-[4-[4-[Bis(2-bromoethyl)amino]benzamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-5-ylcarboxamido]-1-methylpyrrol-5-ylcarboxamido]propionamide hydrobromide



C30-H36-Br2-N12-O4.HBr; Mol wt: 869.41

ACTION – Antineoplastic agent with potent cytotoxic activity *in vitro* against L1210 murine leukemia cells (IC₅₀ = 2.7 ng/ml); it markedly increased survival time in mice bearing L1210 leukemia (%T/C = 750 at 1.56 mg/kg p.o.).

SOURCE – Pharmacia & Upjohn.

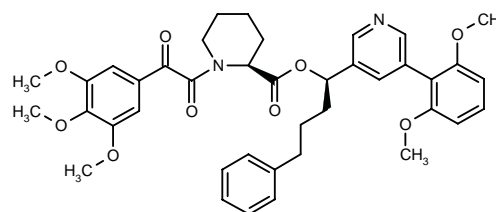
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2. Baraldi, P.G. et al. *PNU 157977: A new potent antitumor agent showing a great increased survival time*. 1st Ital Swiss Meet Med Chem (Sept 23-26, Torino) 1997, Abst B23.

RESISTANCE MODIFIERS

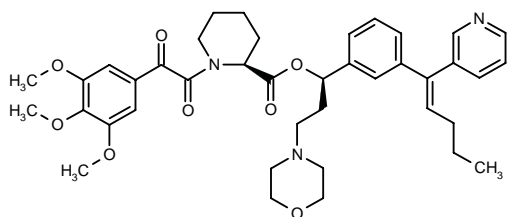
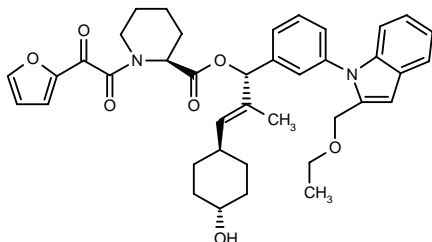
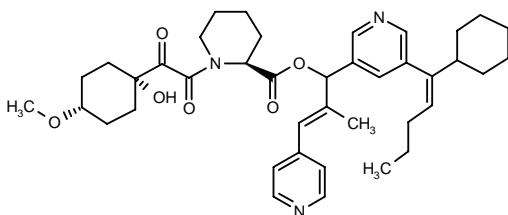
257156

1-[2-(3,4,5-Trimethoxyphenyl)oxalyl]piperidine-2(*S*)-carboxylic acid 1(*R*)-[5-(2,6-dimethoxyphenyl)pyridin-3-yl]-4-phenylbutyl ester



C40-H44-N2-O9; Mol wt: 696.80

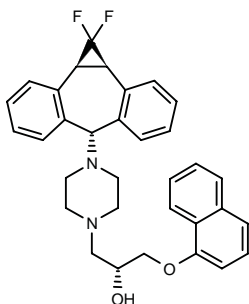
ACTION – Multidrug resistance (MDR)-modulating agent that inhibits MDR-associated protein (MRP)- and P-glycoprotein-mediated MDR. In the presence of 2.5 μM of test compound, the IC₅₀ for doxorubicin against a doxorubicin-resistant strain of murine leukemia L1210 was reduced from 700 nM when used alone to < 50 nM (MDR ratio > 14). The compound also binds to FKBP12 and inhibits FKBP rotomase activity (K_i = 0.5 nM), and it produced an increase in neurite outgrowth in rat pheochromocytoma cells and dorsal root ganglia. Within this series of *N*-(2-oxoacetyl or sulfonyl)-pyrrolidine/piperidine-2-carboxylic acid derivatives, the following are also included:

**259068:** C40-H49-N3-O8**259069:** C39-H44-N2-O7**259070:** C40-H53-N3-O6*SOURCE* – Vertex.**REFERENCES**

1. Armistead, D.M. and Saunders, J.O. (Vertex Pharm., Inc.) *N*-(2 Oxoacetyl or sulphonyl)-pyrrolidine/piperidine-2-carboxylic acid derivs. with improved multi-drug resistance activity. US 5717092, WO 9736869.

258744

anti-1-[4-(1,1-Difluoro-1,1a,6,10b-tetrahydridibenzo-[a,e]cyclopropa[c]cyclohepten-6-yl)piperazin-1-yl]-3-(1-naphthyloxy)-2(*R*)-propanol



C33-H32-F2-N2-O2; Mol wt: 526.62

ACTION – Resistance modulator particularly useful for the treatment of drug-resistant and multidrug-resistant cancer and drug-resistant malaria, reported to act via an interaction with P-glycoprotein. Compound is also useful for enhancing the oral bioavailability or the bioavailability to the brain of a drug.

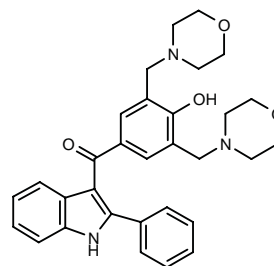
SOURCE – Lilly.**REFERENCES**

1. Kroin, J.S. and Norman, B.H. (Eli Lilly & Co.) *Drug resistance and multidrug resistance modulators*. EP 814081, WO 9748689.

HWL-12**259716**

[4-Hydroxy-3,5-di(morpholin-4-ylmethyl)phenyl](2-phenyl-1*H*-indol-3-yl)methanone

3-[4-Hydroxy-3,5-di(morpholin-4-ylmethyl)benzoyl]-2-phenyl-1*H*-indole



C31-H33-N3-O4; Mol wt: 511.62

ACTION – Multidrug resistance (MDR)-reversing agent proven to be more potent than verapamil in reversing MDR in doxorubicin-resistant human breast carcinoma MCF-7/ADR cells (17.2-fold reversal at 10 μmol/l vs. 8.2-fold reversal at the same concentration of verapamil); it increased cellular doxorubicin accumulation by 3.2-fold at 10 μmol/l in MCF-7/ADR cells, but not in sensitive MCF-7 cells. An effect of the compound on P-glycoprotein was indicated by an increase in Fura-2 accumulation in the Fura 2-AM assay in MCF-7/ADR cells. The compound was originally described as an antiarrhythmic agent.

SOURCES – China Pharm. Univ., Nanjing (CN); Sun Yat-Sen Univ. Med. Sci., Guangzhou (CN).

REFERENCES

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2. Huang, W. et al. *Synthesis and cardiovascular activities of 2-aryl-3-(3',5'-diaminomethyl-4'-hydroxy)benzoylindole derivatives*. Zhongguo Yaowu Huaxue Zazhi 1994, 4(3): 171.

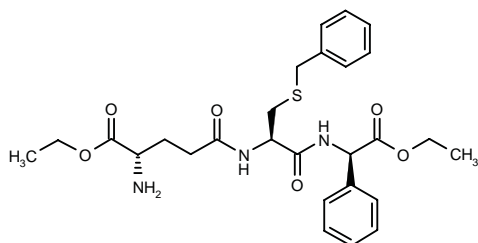
CHEMOPROTECTIVE AGENTS

TER-199

219472

(-)-L- γ -Glutamyl-L-(S-benzyl)cysteinyI-[2(R)-phenyl]-glycine diethyl ester

T.199



C27-H35-N3-O6-S; Mol wt: 529.65

ACTION – Orally active, small-molecule compound that increases the number of bone marrow cells and potentiates the cytotoxic effect of chemotherapeutic agents, potentially useful for protecting against the myelosuppression associated with chemotherapy. The compound is a glutathione analog that specifically inhibits glutathione-S-transferase (GST). It was shown to accelerate postchemotherapy recovery of peripheral neutrophils and platelets in rodent models and enhanced colony formation of human bone marrow cells at concentrations of 0.1-10 μ M.

SOURCE – Terrapin Technologies.

REFERENCES

1. Kauvar, L.M. and Lyttle, M.H. (Terrapin Technol., Inc.) *Glutathione analogs and paralog panels comprising glutathione mimics*. WO 9508563.
2. Kauvar, L.M. et al. (Terrapin Technol., Inc.) *Metabolic effects of certain glutathione analogs*. WO 9640205.
3. Ciaccio, P.J. et al. *Modulation of detoxification gene expression in human colon HT29 cells by glutathione-S-transferase inhibitors*. Amer Soc Pharmacol Exp Ther 1995, 48(4): 639.
4. Kauvar, L.M. *GST-targeted drug candidates*. 1995 Int ISSX - Workshop Glutathione S-transferases (April 22-25, Noordwijkerhout) 1995, Abst L14.
5. Morgan, A.S. et al. *An orally available small molecule stimulator of bone marrow stem cells accelerates postchemotherapy recovery of peripheral neutrophils and platelets*. Proc Amer Assoc Cancer Res 1996, 37: Abst 1961.
6. Schultz, M. et al. *Inhibitors of glutathione S-transferases as therapeutic agents*. Adv Drug Deliv Rev 1997, 26: 91.
7. *Terrapin Technologies raises additional \$3.5 million in private financing - Company also adds new board member*. Terrapin Technologies, Inc. Press Release 1994, December 19.
8. *Terrapin Technologies, Inc. Company Profile*. Terrapin Technologies, Inc. Company Communication 1995, January 4.
9. *Terrapin Technologies, Inc. Oppenheimer & Co., Inc. 6th Annu Health Care Conf* (Nov 8-10, New York) 1995.
10. *Terrapin raises additional \$11.7 million; Clifford Orent is elected chairman of the board*. Terrapin Technologies, Inc. Press Release 1995, November 17.
11. Terrapin Technologies, Inc. Corporate Profile 1995, October.

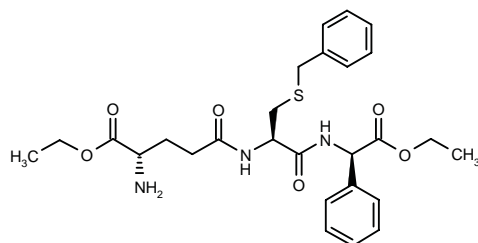
CHEMOPROTECTIVE AGENTS

TER-199

219472

(-)-L- γ -Glutamyl-L-(S-benzyl)cysteinyl-[2(R)-phenyl]-glycine diethyl ester

T.199



C27-H35-N3-O6-S; Mol wt: 529.65

ACTION – Orally active, small-molecule compound that increases the number of bone marrow cells and potentiates the cytotoxic effect of chemotherapeutic agents, potentially useful for protecting against the myelosuppression associated with chemotherapy. The compound is a glutathione analog that specifically inhibits glutathione-S-transferase (GST). It was shown to accelerate postchemotherapy recovery of peripheral neutrophils and platelets in rodent models and enhanced colony formation of human bone marrow cells at concentrations of 0.1-10 μ M.

SOURCE – Terrapin Technologies.

REFERENCES

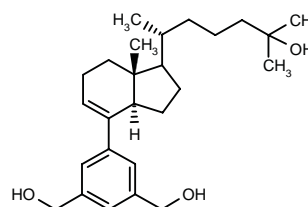
1. Kauvar, L.M. and Lyttle, M.H. (Terrapin Technol., Inc.) *Glutathione analogs and paralog panels comprising glutathione mimics*. WO 9508563.
2. Kauvar, L.M. et al. (Terrapin Technol., Inc.) *Metabolic effects of certain glutathione analogs*. WO 9640205.
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5. Morgan, A.S. et al. *An orally available small molecule stimulator of bone marrow stem cells accelerates postchemotherapy recovery of peripheral neutrophils and platelets*. Proc Amer Assoc Cancer Res 1996, 37: Abst 1961.
6. Schultz, M. et al. *Inhibitors of glutathione S-transferases as therapeutic agents*. Adv Drug Deliv Rev 1997, 26: 91.
7. *Terrapin Technologies raises additional \$3.5 million in private financing - Company also adds new board member*. Terrapin Technologies, Inc. Press Release 1994, December 19.
8. *Terrapin Technologies, Inc. Company Profile*. Terrapin Technologies, Inc. Company Communication 1995, January 4.
9. *Terrapin Technologies, Inc. Oppenheimer & Co., Inc. 6th Annu Health Care Conf* (Nov 8-10, New York) 1995.
10. *Terrapin raises additional \$11.7 million; Clifford Orent is elected chairman of the board*. Terrapin Technologies, Inc. Press Release 1995, November 17.
11. Terrapin Technologies, Inc. Corporate Profile 1995, October.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

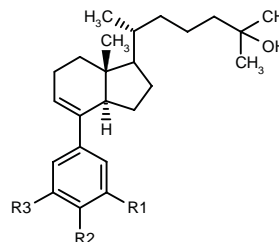
257803

6(R)-[4-[3,5-Bis(hydroxymethyl)phenyl]-7a(R)-methyl-2,3,3a(R),6,7,7a-hexahydro-1H-inden-1-yl]-2-methyl-2-heptanol



C26-H40-O3; Mol wt: 400.60

ACTION – Vitamin D analog for the treatment of osteoporosis, psoriasis and other hyperproliferative skin diseases, certain cancers and immunological disorders, with higher affinity for the calf thymus intracellular vitamin D receptor than calcitriol. Other representative compounds within this series of vitamin D analogs include the following:



Compound	R1	R2	R3	Formula
259072	CH2CH2OH	H	CH2CH2OH	C ₂₈ H ₄₄ O ₃
259073	OH	H	OH	C ₂₄ H ₃₆ O ₃
259074	H	CH2OH	H	C ₂₅ H ₃₈ O ₂
259075	H	CH2CH2OH	H	C ₂₆ H ₄₀ O ₂

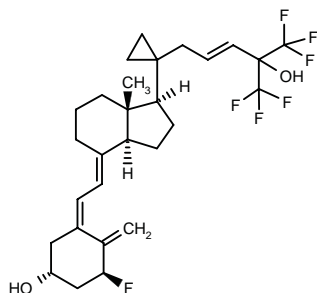
SOURCE – Duphar.

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1. Halkes, S. et al. (Duphar Int. Res. BV) *Vitamin D analogs and methods of preparing these cpds*. WO 9742152.

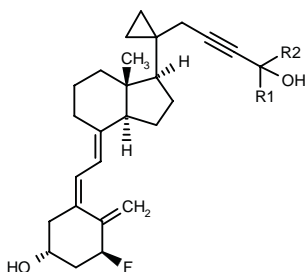
258700

(23*E*)-11 α ,26,26,26,27,27,27-Heptafluoro-25-hydroxy-20,21-methylene-23,24-didehydrovitamin D₃

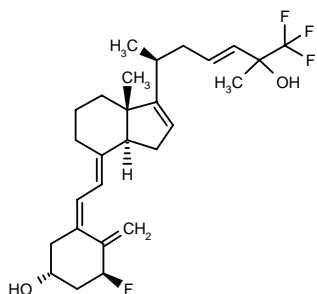


C28-H35-F7-O2; Mol wt: 536.57

ACTION – Vitamin D₃ analog for the treatment of osteoporosis whose activity was demonstrated in ovariectomized rats, where it was about 2-fold more potent than 1,25-dihydroxyvitamin D₃ in increasing bone density following p.o. administration, while it showed reduced calcuric and calcemic effects. Other compounds from this series of fluorinated vitamin D₃ analogs include the following:



Compound	R1=R2	Formula
259426	Me	C ₂₈ H ₃₉ FO ₂
259428	CF ₃	C ₂₈ H ₃₃ F ₇ O ₂



259425: C27-H36-F4-O2

SOURCE – Roche.

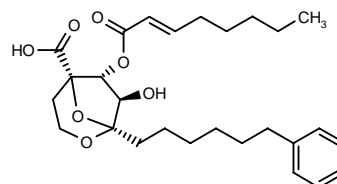
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1. Manchand, P.S. et al. (F. Hoffmann-La Roche AG) *Fluorinated vitamin D₃ analogs*. EP 808832, JP 980945714.

TREATMENT OF LIPOPROTEIN DISORDERS

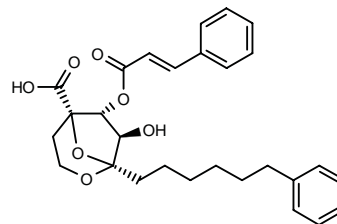
256475

(1*S*,5*S*,6*R*,7*R*)-6-[2(*E*)-Octenoyloxy]-1-(6-phenylhexyl)-2,8-dioxabicyclo[3.2.1]octane-5-carboxylic acid



C27-H38-O7; Mol wt: 474.59

ACTION – Hypolipidemic agent, an inhibitor of squalene synthase (IC₅₀ = 1.1 μM). Another compound from this series of 2,8-dioxabicyclo[3.2.1]octane derivatives is:



260375: C28-H32-O7

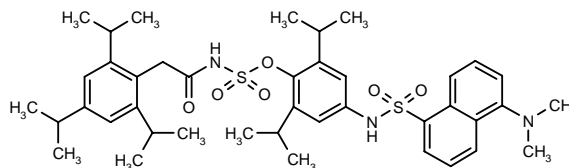
SOURCE – Sagami.

REFERENCES

1. Kobayashi, S. et al. (Sagami Chem. Res. Center) *2,8-Dioxabicyclo[3.2.1]octane derivs*. JP 97227566.

259039

N-[2-(2,4,6-Triisopropylphenyl)acetyl]sulfamic acid 4-[5-(dimethylamino)naphthalen-1-ylsulfonamido]-2,6-diisopropylphenyl ester



C41-H55-N3-O6-S2; Mol wt: 750.02

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of ACAT (IC₅₀ = 10.6 μM in rat liver microsomes) reported to possess improved water solubility and chemical stability over structurally related compounds. *In vivo*, it produced a 61% decrease in total cholesterol at 10 mg/kg p.o. in rats fed a high-cholesterol diet at 10 mg/kg p.o.

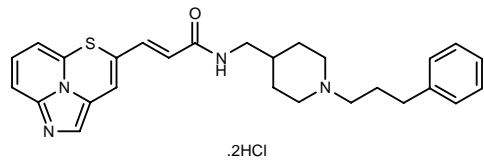
SOURCE – Warner-Lambert.

REFERENCES

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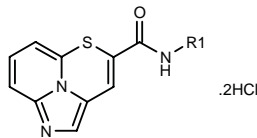
257740

N-[1-(3-Phenylpropyl)piperidin-4-ylmethyl]-3-(5-thia-1,8b-diazaacenaphthylen-4-yl)-2-propenamide dihydrochloride



C27-H30-N4-O-S.2HCl; Mol wt: 531.54

ACTION – Hypolipidemic agent that upregulates LDL receptors, as demonstrated by a 247.4% increase in LDL binding to HepG2 cells at a concentration of 10 μM. Compound demonstrated cholesterol-lowering activity in Golden hamsters, non-HDL cholesterol being 62.3% of control and triglycerides 67.0% of control after an oral dose of 20 mg/kg once daily for 4 days. Also claimed for use in the treatment of atherosclerosis, diabetes and diabetic complications. Other specifically claimed fused imidazopyridine derivatives include the following:



Compound	R1	Formula
259312	(R)-1-(1,4-benzodioxan-2-yl-CH2)-4-Pip-CH2	C ₂₅ H ₂₆ N ₄ O ₃ S.2HCl
259313	4-Ph-1-Pip-(CH2)4	C ₂₅ H ₂₈ N ₄ OS.2HCl
259314	1-[Ph(CH2)3]-4-Pip	C ₂₄ H ₂₆ N ₄ OS.2HCl

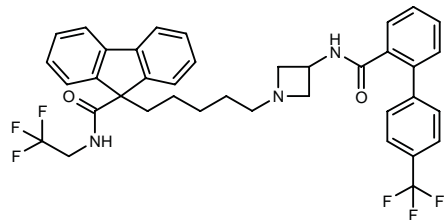
SOURCE – Takeda.

REFERENCES

1. Takatani, M. et al. (Takeda Chem. Ind., Ltd.) *Fused imidazopyridine derivs. as anti-hyperlipidemic agents*. WO 9740051.

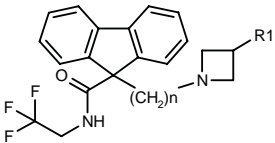
258980

N-(2,2,2-Trifluoroethyl)-9-[5-[3-[4'-(trifluoromethyl)-biphenyl-2-ylcarboxamido]azetidin-1-yl]pentyl]-9H-fluorene-9-carboxamide



C38-H35-F6-N3-O2; Mol wt: 679.70

ACTION – Hypolipidemic and antiatherosclerotic agent that acts by inhibiting microsomal triglyceride transfer protein (MTP). Other specifically claimed compounds include the following:



Compound	R1	n	Formula
259481	NHCOPh	5	C ₃₁ H ₃₂ F ₃ N ₃ O ₂
259482	3-(4-CF3-Ph)-PhCONHCH2	4	C ₃₈ H ₃₅ F ₆ N ₃ O ₂
259483	CH2NHCOPh	4	C ₃₁ H ₃₂ F ₃ N ₃ O ₂
259484	2-(4-CF3-Ph)-PhCONH	4	C ₃₇ H ₃₃ F ₆ N ₃ O ₂
259485	NHCOPh	4	C ₃₀ H ₃₀ F ₃ N ₃ O ₂

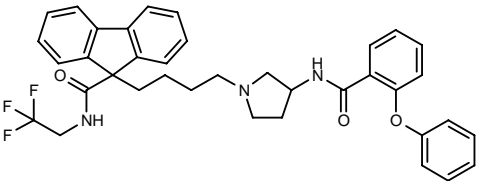
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Biller, S.A. and Dickson, J.K. Jr. (Bristol-Myers Squibb Co.) *Inhibitors of microsomal triglyceride transfer protein and method*. WO 9743255.

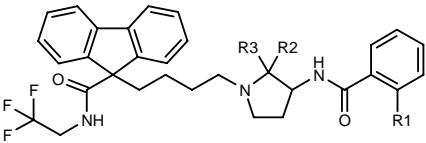
258981

9-[4-[3-(2-Phenoxybenzamido)pyrrolidin-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



C37-H46-F3-N3-O3; Mol wt: 637.78

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of microsomal triglyceride transfer protein (MTP). Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Isomer	Formula
259459	H	H	H		C ₃₁ H ₃₂ F ₃ N ₃ O ₂
259460	OPh	H	H	R	C ₃₇ H ₃₆ F ₃ N ₃ O ₃
259461	OPh	H	H	S	C ₃₇ H ₃₆ F ₃ N ₃ O ₃
259462	4-CF3-Ph	H	H	R	C ₃₈ H ₃₅ F ₆ N ₃ O ₂
259463	4-CF3-Ph	H	H	S	C ₃₈ H ₃₅ F ₆ N ₃ O ₂
259464	4-CF3-Ph	-O-			C ₃₈ H ₃₃ F ₆ N ₃ O ₃
259465	2-benzothiazolyl	-O-			C ₃₈ H ₃₃ F ₃ N ₄ O ₃ S
259466	OPh	-O-			C ₃₇ H ₃₄ F ₃ N ₃ O ₄
259467	H	-O-			C ₃₁ H ₃₀ F ₃ N ₃ O ₃
259468	2-Pyr	-O-			C ₃₈ H ₃₃ F ₃ N ₄ O ₃
259469	4-morpholinyl	H	H		C ₃₅ H ₃₈ F ₃ N ₄ O ₃

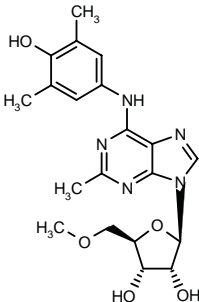
SOURCE – Bristol-Myers Squibb.

REFERENCES

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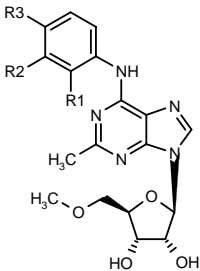
259005

N⁶-(4-Hydroxy-3,5-dimethylphenyl)-2-methyl-5'-O-methyl-adenosine



C20-H25-N5-O5; Mol wt: 415.45

ACTION – Potent and selective adenosine A₁ receptor agonist reported to possess antilipolytic properties and to reduce heart rate and conduction, with potential in the treatment of hyperlipidemias, diabetes, atherosclerosis, cardiac arrhythmias following myocardial infarction, angina, hypertension, heart failure, stroke, CNS disorders, sleep apnea and pain. A representative compound from a series of specifically claimed adenosine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
260026	H	F	OH	C ₁₈ H ₂₀ FN ₅ O ₅
260027	H	H	OH	C ₁₈ H ₂₁ N ₅ O ₅
260028	Me	H	OH	C ₁₉ H ₂₃ N ₅ O ₅
260029	F	H	OH	C ₁₈ H ₂₀ FN ₅ O ₅
260030	H	Cl	OH	C ₁₈ H ₂₀ ClN ₅ O ₅
260031	H	F	F	C ₁₈ H ₁₉ F ₂ N ₅ O ₄
260032	H	H	NHSO ₂ Me	C ₁₉ H ₂₄ N ₆ O ₆ S
260033	H	H	F	C ₁₈ H ₂₀ FN ₅ O ₄
260034	H	F	H	C ₁₈ H ₂₀ FN ₅ O ₄
260035	H	Me	OH	C ₁₉ H ₂₃ N ₅ O ₅
260036	H	Ac	OH	C ₂₀ H ₂₃ N ₅ O ₆
260037	F	H	H	C ₁₈ H ₂₀ FN ₅ O ₄
260038	H	H	i-Pr	C ₂₁ H ₂₇ N ₅ O ₄

SOURCE – Glaxo Wellcome.

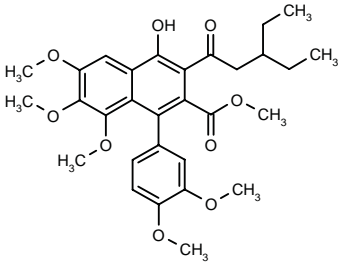
REFERENCES

1. Ellis, F. et al. (Glaxo Group, Ltd.) *Adenosine derivs*. WO 9743300.

S-8921

260565

1-(3,4-Dimethoxyphenyl)-3-(3-ethylpentanoyl)-4-hydroxy-6,7,8-trimethoxy-2-naphthalenecarboxylic acid methyl ester



C30-H36-O9; Mol wt: 540.61

ACTION – Potent and selective ileal Na⁺/bile acid cotransporter (IBAT) inhibitor (IC₅₀ = 66 ± 8 μM for inhibition of [³H]-taurocholate reuptake in COS7 cells expressing cloned hamster IBAT). The compound dose-dependently decreased serum cholesterol and increased fecal bile acid excretion in hamsters when administered in the diet (0.001-0.1%). Similar results were obtained in rats on a high-cholesterol diet at daily doses of 0.1-10.0 mg/kg p.o. Its hypocholesterolemic effect appears to be due to both inhibition of cholesterol absorption in the intestine and enhancement of cholesterol elimination from the body by preventing bile acid reabsorption. Potentially useful for the treatment of hypercholesterolemia or as a pharmacological tool to investigate cholesterol and bile acid metabolism.

SOURCE – Shionogi.

REFERENCES

1. Mori, S. et al. (Shionogi & Co., Ltd.) *Lignan analog, production thereof, and hypolipidemic drug*. EP 597107, JP 93310634, US 5731455, WO 9308155.

2. Mori, S. et al. (Shionogi & Co., Ltd.) *Process for producing lignan cpd*. WO 9424087.

3. Mori, S. et al. (Shionogi & Co., Ltd.) *Lignan cpds*. JP 97241206.

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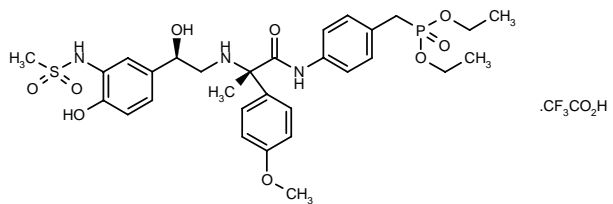
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ANTIOBESITY DRUGS

257191

4-[2(S)-[2(R)-Hydroxy-2-[4-hydroxy-3-(methylsulfonylamido)phenyl]ethylamino]-2-(4-methoxyphenyl)propionamido]benzylphosphonic acid diethyl ester trifluoroacetate



C30-H40-N3-O9-P-S.C2-H-F3-O2; Mol wt: 763.72

ACTION – Antiobesity and antidiabetic agent, a β_3 -adrenoceptor agonist also claimed for use in the treatment of disorders characterized by gastrointestinal hypermotility.

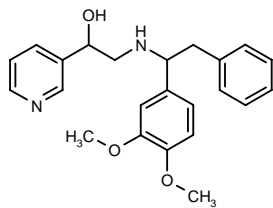
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Cheng, P.T.W. et al. (Bristol-Myers Squibb Co.) *Catecholamine surrogates useful as β_3 agonists*. WO 9737646.

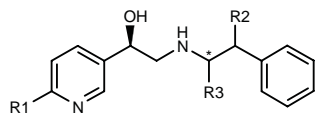
259725

2-[1-(3,4-Dimethoxyphenyl)-2-phenylethylamino]-1-(3-pyridyl)ethanol



C23-H26-N2-O3; Mol wt: 378.47

ACTION – Antiobesity and antidiabetic agent with selective β_3 -adrenoceptor-agonist activity. The compound can also be used to reduce neurogenic inflammation, triglyceride and cholesterol levels and intestinal motility, to increase HDL levels, as well as for the treatment of depression and gastrointestinal disorders. Other compounds from this series of pyridylethanolamine derivatives include the following:



Compound	R1	R2	R3	Formula
259993	H	CON(Me)2	H	C ₁₈ H ₂₃ N ₃ O ₂
259995	H	H	3,4-(MeO)2-Ph	C ₂₃ H ₂₆ N ₂ O ₃
259996	H	H	(R)-3,4-(MeO)2-Ph	C ₂₃ H ₂₆ N ₂ O ₃
259997	H	H	(S)-3,4-(MeO)2-Ph	C ₂₃ H ₂₆ N ₂ O ₃
259999	NH2	H	3,4-(MeO)2-Ph	C ₂₃ H ₂₇ N ₃ O ₃

SOURCE – Merck & Co.

REFERENCES

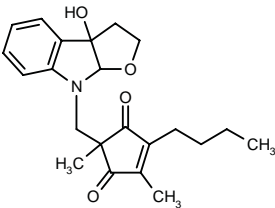
1. Fisher, M.H. et al. (Merck & Co., Inc.) *Selective β_3 agonists for the treatment of diabetes and obesity*. US 5714506.

MADINDOLINE A

241349

4-Butyl-2-(3a-hydroxy-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indol-8-ylmethyl)-2,5-dimethyl-4-cyclopentene-1,3-dione isomer A

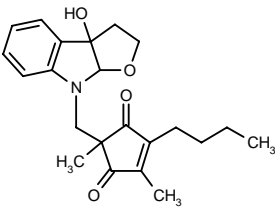
K93-711-A



C22-H27-N-O4; Mol wt: 369.46

Light yellow needles, m.p. 80-4 °C, $[\alpha]_D^{24} +44.4^\circ$ (c 0.3, MeOH).

ACTION – Inhibitor of IL-6 activity isolated from the fermentation broth of *Streptomyces* sp. K93-0711 (FERM P-15253) shown to inhibit the growth of IL-6-dependent MH60 tumor cells ($IC_{50} = 8 \mu M$) but not that of IL-6-independent cell lines. It is suggested to act by inhibiting IL-6 binding to its receptor or the transduction of receptor-associated signals. Potentially useful in the treatment of cancer cachexia, as well as certain tumors. **Madindoline B**, also isolated from this source, is assumed to be a stereoisomer of title compound.



Madindoline B [241350]: C22-H27-N-O4; Isomer B

SOURCE – Kitasato Inst., Tokyo (JP).

REFERENCES

1. Hayashi, M. et al. *Madindoline, a novel inhibitor of IL-6 activity from Streptomyces sp. K93-0711. I. Taxonomy, fermentation, isolation and biological activities*. J Antibiot 1996, 49(11): 1091.

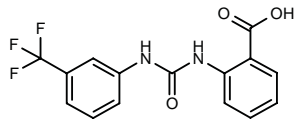
2. Komiya, K. et al. *Cytocidal activity of new antibiotic K93-117-A and -B*. 55th Annu Meet Jpn Cancer Assoc (Oct 10-12, Yokohama) 1996, Abst 697.

3. Takamatsu, S. et al. *Madindolines, novel inhibitors of IL-6 activity from Streptomyces sp. K93-0711. II. Physico-chemical properties and structural elucidation*. J Antibiot 1997, 50(12): 1069.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

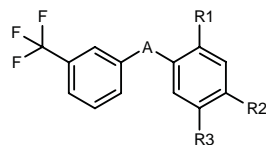
259892

2-[3-[3-(Trifluoromethyl)phenyl]ureido]benzoic acid



C15-H11-F3-N2-O3; Mol wt: 324.26

ACTION – Agent for the treatment of sickle cell anemia, brain edema following ischemia or tumors, diarrhea, hypertension, glaucoma, allergic and inflammatory disorders and for promoting wound healing, a chloride channel blocker (IC_{50} = 0.6 μ M in normal erythrocytes). Other related phenyl derivatives include the following:



Compound	R1	R2	R3	A	Formula
260548	Cl	CO2H	OH	NHCONH	C ₁₅ H ₁₀ ClF ₃ N ₂ O ₄
260549	NH2	H	Cl	NHCONH	C ₁₄ H ₁₁ ClF ₃ N ₃ O
260550	NHSO2Me	H	Cl	NHCONH	C ₁₅ H ₁₃ ClF ₃ N ₃ O ₃ S
260551	i-PrOCO	H	Cl	NHCONH	C ₁₈ H ₁₆ ClF ₃ N ₂ O ₃
260552	CO2H	H	H	CH2CONH	C ₁₆ H ₁₂ F ₃ NO ₃
260553	H	H	CO2H	NHCONH	C ₁₅ H ₁₁ F ₃ N ₂ O ₃
260554	CO2Et	H	H	NHCH2CH2NH	C ₁₈ H ₁₉ F ₃ N ₂ O ₂
260555	CO2H	H	H	NHSO2NH	C ₁₄ H ₁₁ F ₃ N ₂ O ₄ S
260556	CO2H	H	H	CH2NHCONH	C ₁₆ H ₁₃ F ₃ N ₂ O ₃
260557	CO2H	H	H	CONH	C ₁₅ H ₁₀ F ₃ NO ₄

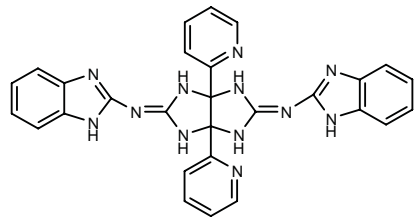
SOURCE – NeuroSearch.

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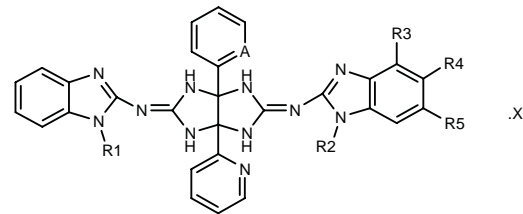
259023

2,5-Bis(1*H*-benzimidazol-2-ylimino)-3a,6a-bis(2-pyridyl)-perhydroimidazo[4,5-*d*]imidazole



C28-H22-N12; Mol wt: 526.56

ACTION – Nonpeptide granulocyte colony-stimulating factor (G-CSF) mimetic, as demonstrated in a luciferase assay using NFS60 cells, where it showed activation above 150% of control in the concentration range 1-32 μ M. Potentially useful for the treatment of neutropenia including chemotherapy-induced neutropenia, and in bone marrow transplantation, as well as for the treatment of bacterial and fungal infections. Other compounds from this series of specifically claimed perhydroimidazo[4,5-*d*]imidazoles include the following:



Compound	R1=R2	R3	R4	R5	A	X	Formula
260299	H	H	H	H	CH		C ₂₉ H ₂₃ N ₁₁
260300	H	Me	H	H	N		C ₂₉ H ₂₄ N ₁₂
260301	H	H	Me	H	N	2CF3CO2H	C ₂₉ H ₂₄ N ₁₂ .2C ₂ HF ₃ O ₂
260302	Me	H	H	H	N	2CF3CO2H	C ₃₀ H ₂₆ N ₁₂ .2C ₂ HF ₃ O ₂
260303	H	H	Me	Me	N	2CF3CO2H	C ₃₀ H ₂₆ N ₁₂ .2C ₂ HF ₃ O ₂

SOURCE – SmithKline Beecham.

REFERENCES

1. Luengo, J.I. et al. (SmithKline Beecham Corp.) *Non-peptide G-CSF mimetics*. WO 9744033.

δ-EKLF

260094

δ-Erythroid krüppel-like factor

ACTION – Modified form of the β-erythroid krüppel-like factor (β-EKLF) that binds to the wild-type δ-globin promoter, resulting in increased δ-globin expression. A nucleic acid encoding this polypeptide can be used to induce δ-globin gene expression in a cell, preferably a pluripotent hematopoietic stem cell, for use in the gene therapy of hemoglobinopathies such as sickle cell anemia and β-thalassemia.

SOURCE – UAB Res. Found., Birmingham, AL (US).

REFERENCES

1. Townes, T.M. and Donze, D. (The UAB Res. Found.) *δ-Erythroid krüppel-like factors and methods of use*. WO 9747306.

OPRELVEKIN

Prop INN; USAN

196733

2-178-Interleukin 11 (human clone pXM/IL-11)

IL-11+
rhIL-11
YM-294

C854-H1411-N253-O235-S2; Mol wt: 19047.21

ACTION – Recombinant form of human interleukin-11 (rhIL-11), a naturally occurring platelet growth factor.

INDICATION – Prevention of severe thrombocytopenia and reduction of the need for platelet transfusions following myelosuppressive chemotherapy in patients with non-myeloid malignancies who are at high risk of severe thrombocytopenia.

PRESENTATION – Vials, 5 mg oprelvekin as lyophilized powder for dilution in 5 ml sterilized water.

PROPRIETARY NAME – Neumega (US).

SOURCE – Genetics Inst.

RECENT REFERENCES

1. Albert, L. et al. *Recombinant human interleukin eleven decreases adjuvant-induced arthritis in Lewis rats.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 145.

2. Aoyama, K. et al. *Pharmacokinetics of recombinant human interleukin-11 (rhIL-11) in healthy male subjects.* Brit J Clin Pharmacol 1997, 43(6): 571.

3. Bank, S. et al. *Safety and activity evaluation of rhIL-11 in subjects with active Crohn's disease.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 3526.

4. Bozza, M. et al. *rhIL-11 does not modulate purified human neutrophil function in culture.* Blood 1997, 90(10, Suppl. 1, Part 2): Abst 2868.

5. Collins, M. et al. *rhIL-11 and thrombopoietin synergize to improve platelet recovery in mice treated with a combined modality regimen of carboplatin and irradiation.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 758.

6. Du, X. and Williams, D.A. *Interleukin-11. Review of molecular, cell biology, and clinical use.* Blood 1997, 89(11): 3897.

7. Dykstra, K.H. et al. *A mathematical model of the kinetics of platelet production after high-dose chemotherapy and treatment with Neumega® (rhIL-11).* Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3553.

8. Gordon, M.S. et al. *A phase I trial of recombinant human interleukin-11 (Neumega rhIL-11 growth factor) in women with breast cancer receiving chemotherapy.* Blood 1996, 87(9): 3615.

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10. Keith, J.C. Jr. *Beneficial effects of interleukin-11 in animal models of Crohn's disease.* IBC Conf Dev Novel Anti-Inflamm Ther Inflamm Bowel Dis (June 3-4, Philadelphia) 1996.

11. Kirov, I. et al. *Recombinant human interleukin 11 (Neumega®) is tolerated at double the adult dose and enhances hematopoietic recovery following ifosfamide, carboplatin and etoposide (ICE) chemotherapy in children: Correlation with rapid clearance, lack of induction of inflammatory cytokines and mobilization of early progenitor cells.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 2584.

12. Lu, L. et al. *Effect of recombinant human interleukin 11 in combination with other cytokines on megakaryocytic progenitors in CD34+ cord blood, mobilized peripheral blood and bone marrow cells.* Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3379.

13. Opal, S.M. *The utility of recombinant human interleukin-11 (rhIL-11) in the prevention of sepsis.* IBC Conf 6th Annu Symp. Sepsis Adv Treat Drug Dev (June 24-26, Cambridge) 1996.

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15. Orazi, A. et al. *Effects of recombinant human interleukin-11 (Neumega™) rhIL-11 growth factor) on megakaryocytopoiesis in human bone marrow.* Exp Hematol 1996, 24(11): 1289.

16. Smith, J.W. II. et al. *Integrated analysis of two placebo-controlled studies of Neumega® (rhIL-11) to prevent severe chemotherapy-induced thrombocytopenia.* Proc Amer Soc Clin Oncol 1997, 16: Abst 388.

17. Tepler, I. et al. *A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy.* Blood 1996, 87(9): 3607.

18. *Breast cancer chemotherapy study finds that rhIL-11 reduces need for platelet transfusions by 60%.* Genetics Institute, Inc. Press Release 1996, May 15.

19. *First marketing approval granted for Neumega.* Prous Science Daily Essentials November 26, 1997.

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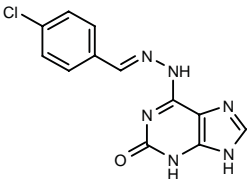
21. *rhIL-11 sees first launch.* Prous Science Daily Essentials February 17, 1998.

*Drug Data Rep 1993, 15(8): 744.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

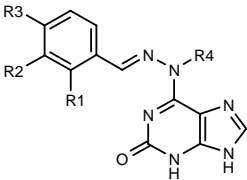
258725

6-(4-Chlorobenzylidenehydrazino)-2,3-dihydro-9H-purin-2-one

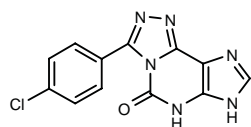


C12-H9-Cl-N6-O; Mol wt: 288.70

ACTION – Agent for the treatment of hyperuricemia and gout, a xanthine oxidase inhibitor (IC₅₀ = 0.025 µM using bovine milk-derived enzyme; IC₅₀ allopurinol > 10 µM). Within this series of purine and triazolopurine compounds, the following are also included:



Compound	R1	R2	R3	R4	Formula
259144	H	H	F	H	C ₁₂ H ₉ FN ₆ O
259145	H	H	N(Me) ₂	H	C ₁₄ H ₁₅ N ₇ O
259146	H	H	NO ₂	H	C ₁₂ H ₉ N ₇ O ₃
259147	H	H	OMe	H	C ₁₃ H ₁₂ N ₆ O ₂
259148	H	-OCH ₂ O-		H	C ₁₃ H ₁₀ N ₆ O ₃
259149	H	H	OH	H	C ₁₂ H ₁₀ N ₆ O ₂
259150	OMe	H	H	Me	C ₁₄ H ₁₄ N ₆ O ₂
259151	H	OMe	H	Me	C ₁₄ H ₁₄ N ₆ O ₂
259152	H	H	OMe	Me	C ₁₄ H ₁₄ N ₆ O ₂
259153	H	H	F	Me	C ₁₃ H ₁₁ FN ₆ O
259154	H	H	OH	Me	C ₁₃ H ₁₂ N ₆ O ₂



259155: C12-H7-Cl-N6-O

SOURCE – Yamasa Corp.

REFERENCES

1. Nagamatsu, T. et al. (Yamasa Corp.) *Purine cpds. and xanthine oxidase inhibitors*. EP 811624, WO 9626208.

DIAGNOSTIC AGENTS

FS069+

219358

Perfluoropropane-filled albumin microspheres (mean diameter 2.0-4.5 μm , concentration 5.0-8.0 $\times 10^8$ microspheres/ml) produced by sonication

FS-069

ACTION – Ultrasound imaging agent.

INDICATION – To opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders in patients with suboptimal echocardiograms.

PRESENTATION – Single-use vials (3 ml), each ml containing 5.0-8.0 $\times 10^8$ human albumin microspheres, 10 mg Albumin Human USP, 0.22 \pm 0.11 mg/ml octafluoropropane.

PROPRIETARY NAME – Optison (US).

SOURCES – Molecular Biosystems; marketed by Mallinckrodt.

RECENT REFERENCES

1. Aronson, S. et al. *Assessment of regional renal blood flow in the dog with FS069, a novel intravenous ultrasound contrast agent*. Anesth Analg 1996, 82(2, Suppl.): Abst S10.
2. Aronson, S. et al. *Monitoring changes in renal blood flow resistance with intravenous contrast ultrasound*. Anesthesiology 1996, 85(3A): Abst A273.
3. Cohen, J. et al. *A multicenter trial comparing FS069 and Albunex® for left ventricular endocardial border delineation*. J Amer Coll Cardiol 1997, 29(2, Suppl. A): Abst 1094-25.
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6. Greener, Y. et al. *Safety and efficacy of FS069, a novel ultrasound (US) contrast agent for myocardial perfusion in the anesthetized canine model*. J Cardiovasc Diagn Proc 1996, 13(1): 67.
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11. Kovacich, D. et al. *Endocardial visualization using 2D imaging, Albunex and FS069*. Circulation 1996, 94(8, Suppl.): Abst 2623.

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13. Main, M.L. et al. *Contrast echo detection of flow limiting coronary stenoses using FS069 with second harmonic transient response imaging*. Circulation 1996, 94(8, Suppl.): Abst 3360.

14. Meltzer, R.S. et al. *New echocardiographic contrast agents for myocardial perfusion imaging*. J Cardiovasc Diagn Proc 1996, 13(1): 86.

15. Meza, M. et al. *Myocardial contrast echocardiography: Reliable, safe, and efficacious myocardial perfusion assessment after intravenous injections of a new echocardiographic contrast agent*. Am Heart J 1996, 132(4): 871.

16. Mills, J.D. et al. *Transient response second harmonic imaging using intravenous FS069 can quantify coronary stenoses without the need for pharmacologic stress*. J Amer Coll Cardiol 1997, 29(2, Suppl. A): Abst 764-1.

17. Mobarek, S. et al. *Adenosine reduces micro-vascular damage in the post-reperfusion period: A myocardial contrast echocardiography study*. J Amer Coll Cardiol 1996, 27(2, Suppl. A): Abst 1040-68.

18. Mobarek, S. et al. *Assessment of renal perfusion in a canine model using FS069, a new transpulmonary echo-contrast agent*. J Invest Med 1996, 44(1): 54A.

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20. Mor-Avi, V. et al. *Echocardiographic contrast agents and left ventricular contractility: Evaluation using an isolated rabbit heart model*. J Am Soc Echocardiogr 1996, 9(4): 452.

21. Richards, D.R. et al. *Myocardial contrast echocardiography: Comparison of sensitivity and specificity of FS069 vs. thallium-201 in detecting myocardial ischemia and heterogeneous perfusion*. J Amer Coll Cardiol 1996, 27(2, Suppl. A): Abst 1040-67.

22. Roth, S. et al. *Contrast ultrasound imaging of the ocular circulation*. Invest Ophthalmol Visual Sci 1996, 37(3): Abst 3880.

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25. *European approval recommended for Optison*. Prous Science Daily Essentials January 30, 1998.

26. *FDA advisory panel recommends approval for ultrasound imaging agent, FS069*. Molecular Biosystems, Inc. Press Release 1997, February 25.

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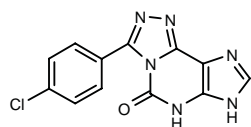
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259155: C12-H7-Cl-N6-O

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219358

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37. *Molecular Biosystems reports third quarter financial results.* Molecular Biosystems, Inc. Press Release 1996, February 7.

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40. *Phase 2 FS069 myocardial contrast echo results presented at the American College of Cardiology.* Molecular Biosystems, Inc. Press Release 1996, March 27.

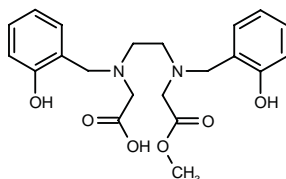
*Drug Data Rep 1997, 19(6): 574.

TREATMENT OF POISONING AND DRUG DEPENDENCY

259038

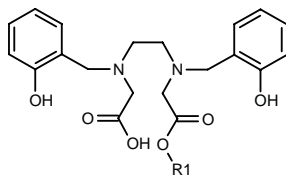
2-[N-(2-Hydroxybenzyl)-N-[2-[N-(2-hydroxybenzyl)-N-(methoxycarbonylmethyl)amino]ethyl]amino]acetic acid

3,6-Bis(2-hydroxybenzyl)-3,6-diazaoctanedioic acid monomethyl ester



C21-H26-N2-O6; Mol wt: 402.45

ACTION – Trivalent metal-chelating agent with potential in the treatment of diseases characterized by excess iron, reported to possess high affinity for iron, excellent absorption following oral administration and to be well tolerated even at high doses. Other specifically claimed compounds include the following:



Compound	R1	Formula
260268	Et	C ₂₂ H ₂₈ N ₂ O ₆
260269	CH(i-Pr)OAc	C ₂₆ H ₃₄ N ₂ O ₈

SOURCE – Novartis.

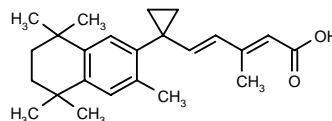
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PHARMACOLOGICAL TOOLS

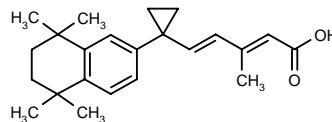
256888

3-Methyl-5-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]-2(E),4(E)-pentadienoic acid



C24-H32-O2; Mol wt: 352.52

ACTION – Potent and selective retinoid X receptor (RXR) agonist ($K_i = 4, 4$ and 5 nM, respectively, for displacement of [³H]-9-*cis*-retinoic acid binding at RXR α , RXR β and RXR γ receptor subtypes) with low affinity for the retinoic acid receptor ($K_i > 1000$ nM for displacement of [³H]-*all-trans*-retinoic acid binding to RAR α , RAR β and RAR γ receptors). The compound was also found to be a potent RXR agonist in cotransfection assays ($EC_{50} = 5, 13$ and 7 nM, respectively, for RXR α , RXR β and RXR γ receptor subtypes), with little or no activity at RAR receptors. Another conformationally restricted RXR-selective retinoid is:



256889: C23-H30-O2

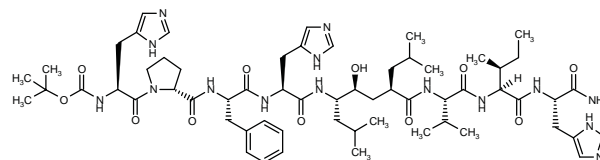
SOURCE – Ligand.

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259854

tert-Butoxycarbonyl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucyl-ψ[(S)-CH(OH)CH₂]-L-leucyl-L-valyl-L-isoleucyl-L-histidinamide



C61-H93-N15-O11; Mol wt: 1212.50

ACTION – Potent renin inhibitor both *in vitro* ($IC_{50} = 1.0$ and 4.8 nM against rat and human plasma renin, respectively) and *in vivo*, where the compound was able to reduce mean arterial pressure in a renin-dependent model of hypertension in rats (to 129.0 ± 12.9 mmHg during infusion of 1.0 mg/kg/h from a preinfusion value of 193.8 ± 2.0 mmHg in two-kidney, one-clip hypertensive rats), simultaneously suppressing both plasma renin and angiotensin II. Potentially useful as a tool for investigating the relative involvement of circulatory and extracirculatory renin in the pathogenesis of hypertension. Another angiotensinogen analog with high selectivity for rat vs. human renin is:

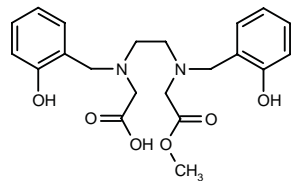
35. *Molecular Biosystems, Mallinckrodt Group announce completion of phase 3 clinical trial on ultrasound contrast agent, FS069.* Molecular Biosystems, Inc. Press Release 1996, April 1.
36. *Molecular Biosystems' Optison reclassified as drug.* Prous Science Daily Essentials July 30, 1997.
37. *Molecular Biosystems reports third quarter financial results.* Molecular Biosystems, Inc. Press Release 1996, February 7.
38. *Optison evaluated in phase II trials for myocardial perfusion imaging.* Prous Science Daily Essentials August 19, 1997.
39. *Optison imaging agent launched in U.S.* Prous Science Daily Essentials January 29, 1998.
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- *Drug Data Rep 1997, 19(6): 574.

TREATMENT OF POISONING AND
DRUG DEPENDENCY

259038

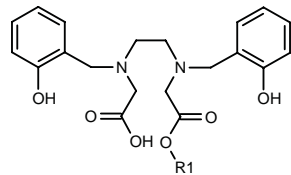
2-[N-(2-Hydroxybenzyl)-N-[2-[N-(2-hydroxybenzyl)-N-(methoxycarbonylmethyl)amino]ethyl]amino]acetic acid

3,6-Bis(2-hydroxybenzyl)-3,6-diazaoctanedioic acid monomethyl ester



C21-H26-N2-O6; Mol wt: 402.45

ACTION – Trivalent metal-chelating agent with potential in the treatment of diseases characterized by excess iron, reported to possess high affinity for iron, excellent absorption following oral administration and to be well tolerated even at high doses. Other specifically claimed compounds include the following:



Compound	R1	Formula
260268	Et	C ₂₂ H ₂₈ N ₂ O ₆
260269	CH(i-Pr)OAc	C ₂₆ H ₃₄ N ₂ O ₈

SOURCE – Novartis.

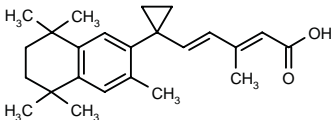
REFERENCES

1. Spanka, C. and Bühlmayer, P. (Novartis AG) *N,N'-Di(2-hydroxybenzyl)ethylene-diamine-N,N'-diacetic acid derivs.* WO 9744313.

PHARMACOLOGICAL TOOLS

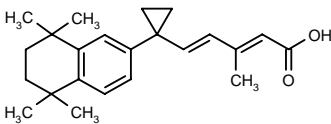
256888

3-Methyl-5-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]-2(E),4(E)-pentadienoic acid



C24-H32-O2; Mol wt: 352.52

ACTION – Potent and selective retinoid X receptor (RXR) agonist ($K_i = 4, 4$ and 5 nM, respectively, for displacement of [3 H]-9-*cis*-retinoic acid binding at RXR α , RXR β and RXR γ receptor subtypes) with low affinity for the retinoic acid receptor ($K_i > 1000$ nM for displacement of [3 H]-*all-trans*-retinoic acid binding to RAR α , RAR β and RAR γ receptors). The compound was also found to be a potent RXR agonist in cotransfection assays ($EC_{50} = 5, 13$ and 7 nM, respectively, for RXR α , RXR β and RXR γ receptor subtypes), with little or no activity at RAR receptors. Another conformationally restricted RXR-selective retinoid is:



256889: C23-H30-O2

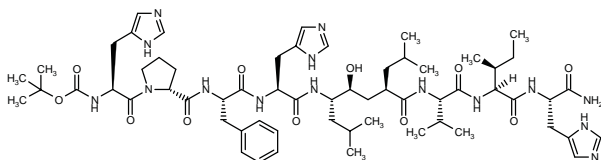
SOURCE – Ligand.

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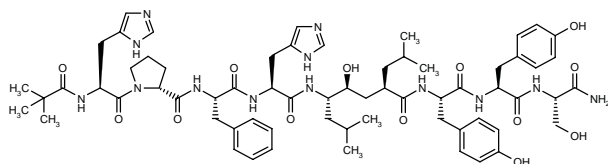
259854

tert-Butoxycarbonyl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucyl-ψ[(*S*)-CH(OH)CH₂]-L-leucyl-L-valyl-L-isoleucyl-L-histidinamide



C61-H93-N15-O11; Mol wt: 1212.50

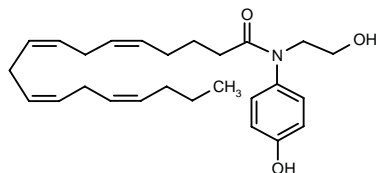
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**259855:** C65-H89-N13-O13**SOURCE** – Ferring.**REFERENCES**

1. Sueiras-Diaz, J. et al. *Potent in vivo inhibitors of rat renin: Analogues of human and rat angiotensinogen sequences containing different classes of pseudodipeptides at the scissile site.* Peptide Res 1997, 50(4): 239.

AM-404**259083**

(*all-Z*)-*N*-(2-Hydroxyethyl)-*N*-(4-hydroxyphenyl)-5,8,11,14-eicosatetraenamide



C28-H41-N-O3; Mol wt: 439.64

ACTION – Competitive inhibitor of carrier-mediated anandamide transport proven to inhibit high-affinity anandamide accumulation in cultured neurons ($IC_{50} = 1 \mu M$) and astrocytes ($IC_{50} = 5 \mu M$) from rat embryos. AM-404 enhances cannabinoid receptor-mediated anandamide responses both *in vivo* and *in vitro*, although it does not activate cannabinoid receptors or inhibit anandamide hydrolysis. Potentially useful as a tool for elucidating the physiological roles of the cannabinoid system, and also as a lead for the development of therapeutic agents.

SOURCES – Univ. Connecticut, Storrs, CT (US); Univ. Naples, Naples (IT); Neurosci Inst., San Diego, CA (US).

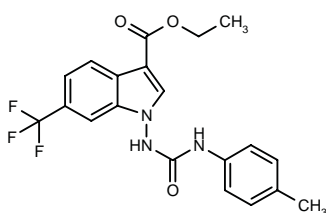
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1. Beltramo, M. et al. *Functional role of high-affinity anandamide transport, as revealed by selective inhibition.* Science 1997, 277: 1094.

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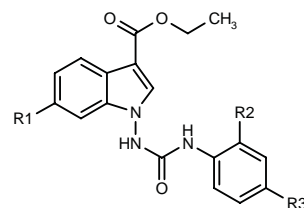
CGS-7181**259846**

1-[3-(4-Methylphenyl)ureido]-6-(trifluoromethyl)indole-3-carboxylic acid ethyl ester



C20-H18-F3-N3-O3; Mol wt: 405.38

ACTION – Potent large-conductance Ca^{2+} -activated K^{+} (BK_{Ca}) channel opener with a combination of potency and efficacy superior to known BK_{Ca} channel openers such as NS-004 and DHS-1. Other related compounds with similar potency, efficacy and pharmacological profile are:



Compound	R1	R2	R3	Formula
CGS-7184 [259858]	CF3	H	Cl	$C_{19}H_{15}ClF_3N_3O_3$
CGS-7590 [259859]	CF3	H	SMe	$C_{20}H_{18}F_3N_3O_3S$
CGS-7725 [259860]	Cl	F	H	$C_{18}H_{15}ClFN_3O_3$

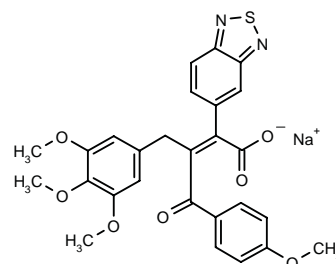
SOURCE – Novartis.**REFERENCES**

1. Hu, S. et al. *Novel and potent BK channel openers: CGS 7181 and its analogs.* Drug Develop Res 1997, 41(1): 10.

2. Hu, S. et al. *Novel and potent BK channel openers CGS 7181 and its analogs.* Pflug Arch Eur J Physiol 1997, 434(5, Suppl.): R102.

EMD-122801***258862****255072** (as free acid)**256225** (as lactone form)

2-(2,1,3-Benzothiadiazol-5-yl)-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-2-butenic acid sodium salt



C27-H23-N2-Na-O7-S; Mol wt: 542.54

ACTION – Potent, selective, stable, water-soluble endothelin ET_A receptor antagonist, as shown in binding ($IC_{50} = 0.30$ and 340.0 nM, respectively, for ET_A and ET_B receptors) and functional assays ($pA_2 = 8.5$ for antagonism of ET-1-induced contractions in isolated rat aortic rings without endothelium). This compound bears a benzothiadiazole group instead of a methylenedioxyphenyl group and is thus expected to be devoid of the undesirable metabolic interactions with cytochrome P-450 ascribed to the latter functionality. Potentially useful for evaluating the benefit of ET_A receptor antagonism in endothelin-related diseases.

SOURCE – Merck KGaA.

REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *2,1,3-Benzothia(oxa)diazole derivs. having an endothelin receptor antagonistic effect*. DE 19607096, WO 9730982.

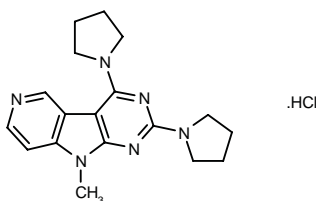
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*Identified compound **255072** Drug Data Rep 1997, 19(11): 986.

PNU-107484A

259353

9-Methyl-2,4-di(1-pyrrolidinyl)-9H-pyrido[3',4':4,5]pyrrolo-[2,3-*d*]pyrimidine hydrochloride



C18-H22-N6.HCl; Mol wt: 358.87

ACTION – Novel GABA_A receptor ligand with α isoform-dependent functionalities. PNU-107484A enhanced GABA-induced Cl⁻ currents in the $\alpha 1\beta 2\gamma 2$ subtype of GABA_A receptor ($EC_{50} = 3.1 \pm 0.5 \mu M$), but the opposite effect was found for $\alpha 3\beta 2\gamma 2$ and $\alpha 6\beta 2\gamma 2$ subtypes ($IC_{50} = 4.2 \pm 1$ and $3.5 \pm 0.2 \mu M$, respectively). PNU-107484A behaved like a positive allosteric modulator of the $\alpha 1\beta 2\gamma 2$ subtype, while it behaved like a negative allosteric modulator of the GABA $\alpha 3\beta 2\gamma 2$ and $\alpha 6\beta 2\gamma 2$ receptor subtypes. Compound may be useful for the development of α isoform-selective ligands, and it may provide a new tool for investigating the physiological roles of the various α isoforms.

SOURCE – Pharmacia & Upjohn.

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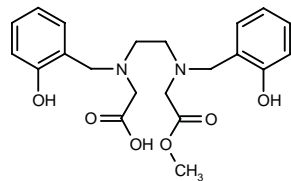
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TREATMENT OF POISONING AND
DRUG DEPENDENCY

259038

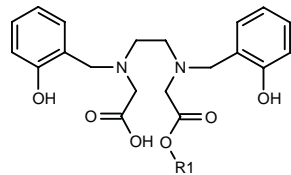
2-[N-(2-Hydroxybenzyl)-N-[2-[N-(2-hydroxybenzyl)-N-(methoxycarbonylmethyl)amino]ethyl]amino]acetic acid

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260269	CH(i-Pr)OAc	C ₂₆ H ₃₄ N ₂ O ₈

SOURCE – Novartis.

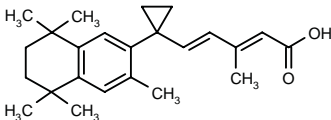
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PHARMACOLOGICAL TOOLS

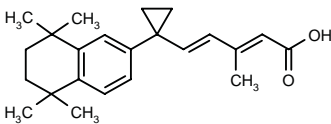
256888

3-Methyl-5-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]-2(E),4(E)-pentadienoic acid



C24-H32-O2; Mol wt: 352.52

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256889: C23-H30-O2

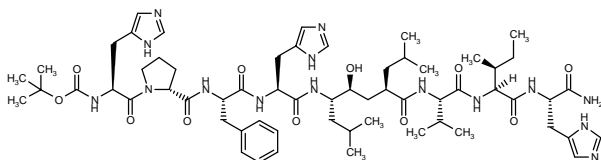
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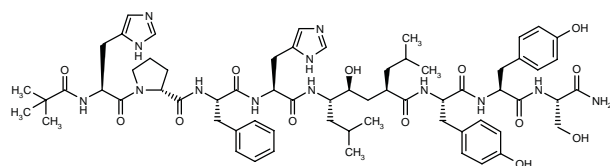
259854

tert-Butoxycarbonyl-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucyl-ψ[(*S*)-CH(OH)CH₂]-L-leucyl-L-valyl-L-isoleucyl-L-histidinamide



C61-H93-N15-O11; Mol wt: 1212.50

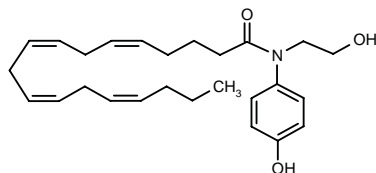
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AM-404**259083**

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C28-H41-N-O3; Mol wt: 439.64

ACTION – Competitive inhibitor of carrier-mediated anandamide transport proven to inhibit high-affinity anandamide accumulation in cultured neurons ($IC_{50} = 1 \mu M$) and astrocytes ($IC_{50} = 5 \mu M$) from rat embryos. AM-404 enhances cannabinoid receptor-mediated anandamide responses both *in vivo* and *in vitro*, although it does not activate cannabinoid receptors or inhibit anandamide hydrolysis. Potentially useful as a tool for elucidating the physiological roles of the cannabinoid system, and also as a lead for the development of therapeutic agents.

SOURCES – Univ. Connecticut, Storrs, CT (US); Univ. Naples, Naples (IT); Neurosci Inst., San Diego, CA (US).

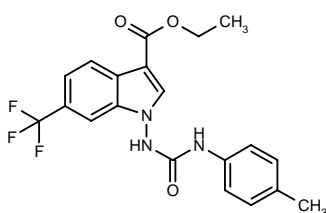
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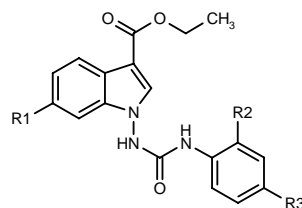
CGS-7181**259846**

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C20-H18-F3-N3-O3; Mol wt: 405.38

ACTION – Potent large-conductance Ca^{2+} -activated K^+ (BK_{Ca}) channel opener with a combination of potency and efficacy superior to known BK_{Ca} channel openers such as NS-004 and DHS-1. Other related compounds with similar potency, efficacy and pharmacological profile are:



Compound	R1	R2	R3	Formula
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CGS-7590 [259859]	CF3	H	SMe	$C_{20}H_{18}F_3N_3O_3S$
CGS-7725 [259860]	Cl	F	H	$C_{18}H_{15}ClFN_3O_3$

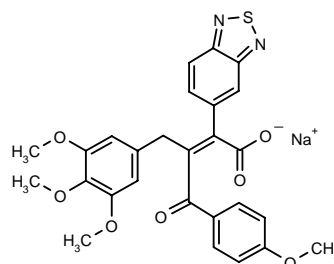
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EMD-122801***258862****255072** (as free acid)**256225** (as lactone form)

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C27-H23-N2-Na-O7-S; Mol wt: 542.54

ACTION – Potent, selective, stable, water-soluble endothelin ET_A receptor antagonist, as shown in binding ($IC_{50} = 0.30$ and 340.0 nM, respectively, for ET_A and ET_B receptors) and functional assays ($pA_2 = 8.5$ for antagonism of ET-1-induced contractions in isolated rat aortic rings without endothelium). This compound bears a benzothiadiazole group instead of a methylenedioxyphenyl group and is thus expected to be devoid of the undesirable metabolic interactions with cytochrome P-450 ascribed to the latter functionality. Potentially useful for evaluating the benefit of ET_A receptor antagonism in endothelin-related diseases.

SOURCE – Merck KGaA.

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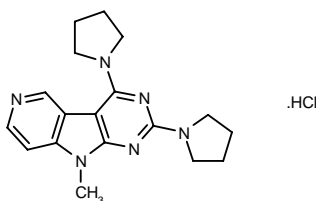
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*Identified compound **255072** Drug Data Rep 1997, 19(11): 986.

PNU-107484A

259353

9-Methyl-2,4-di(1-pyrrolidinyl)-9H-pyrido[3',4':4,5]pyrrolo-[2,3-*d*]pyrimidine hydrochloride



C18-H22-N6.HCl; Mol wt: 358.87

ACTION – Novel GABA_A receptor ligand with α isoform-dependent functionalities. PNU-107484A enhanced GABA-induced Cl⁻ currents in the α 1 β 2 γ 2 subtype of GABA_A receptor ($EC_{50} = 3.1 \pm 0.5 \mu M$), but the opposite effect was found for α 3 β 2 γ 2 and α 6 β 2 γ 2 subtypes ($IC_{50} = 4.2 \pm 1$ and $3.5 \pm 0.2 \mu M$, respectively). PNU-107484A behaved like a positive allosteric modulator of the α 1 β 2 γ 2 subtype, while it behaved like a negative allosteric modulator of the GABA α 3 β 2 γ 2 and α 6 β 2 γ 2 receptor subtypes. Compound may be useful for the development of α isoform-selective ligands, and it may provide a new tool for investigating the physiological roles of the various α isoforms.

SOURCE – Pharmacia & Upjohn.

REFERENCES

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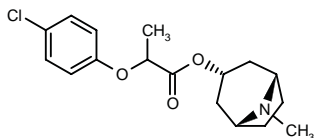
ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

ET-142

261286

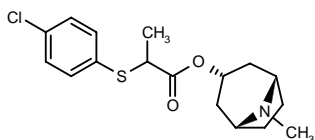
endo-2-(4-Chlorophenoxy)propionic acid 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester



C17-H22-Cl-N-O3; Mol wt: 323.82

Maleate salt, m.p. 112-4 °C.

ACTION – Cholinergic modulator structurally related to atropine with weak acetylcholinesterase-inhibitory activity ($IC_{50} = 0.3$ mM using electrical eel enzyme). It exhibited antinociceptive properties in mice using the hot-plate test ($ED_{50} = 32 \pm 2.3$ mg/kg s.c.; effective dose range upon i.c.v. administration of 10-30 μ g) and the acid acetic-induced abdominal constriction test (10-20 mg/kg s.c.), as well as in rats using the paw pressure test (20-40 mg/kg i.p.), with no apparent disruptive effect on behavior; the increase in pain threshold could be prevented by atropine, dicyclomine, pirenzepine and hemicholinium-3. In functional studies *in vitro*, ET-142 enhanced electrically evoked contractions of guinea pig ileum myenteric plexus longitudinal muscle strips at concentrations of 1 pM-1 nM, inducing inhibition at 1-10 μ M. Another related compound with a similar pharmacological profile is:



SS-20 [261287]: C17-H22-Cl-N-O2-S

SOURCE – Fidia.

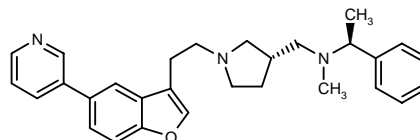
REFERENCES

1. Bartolini, A. et al. (Fidia SpA) *New analgesic and nootropic drugs*. EP 650486, JP 95508739, US 5583142, WO 9401435.
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3. Gualtieri, F. et al. *Presynaptic cholinergic modulators as potent cognition enhancers and analgesic drugs. 2-Phenoxy-, 2-(phenylthio)-, and 2-(phenylamino)alkanoic acid esters*. J Med Chem 1994, 37(11): 1712.

ANTIMIGRAINE DRUGS

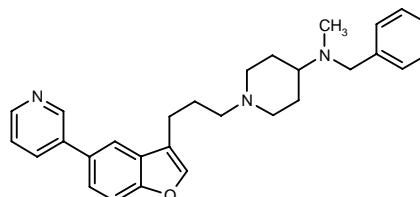
259864

N-Methyl-*N*-[1(*S*)-phenylethyl]-*N*-[1-[2-[5-(3-pyridyl)-benzofuran-3-yl]ethyl]pyrrolidin-3(*R*)-ylmethyl]amine



C29-H33-N3-O; Mol wt: 439.60

ACTION – Antimigraine agent, a 5-HT_{1D} receptor agonist with selective affinity for the 5-HT_{1Dα} (5-HT_{1D}) receptor subtype relative to the 5-HT_{1Dβ} (5-HT_{1B}) receptor subtype and thus associated with fewer side effects, notably adverse cardiovascular events, relative to non-subtype-selective 5-HT_{1D} agonists. Another specifically claimed compound within this series of azetidine, pyrrolidine and piperidine derivatives is:



260642: C29-H33-N3-O

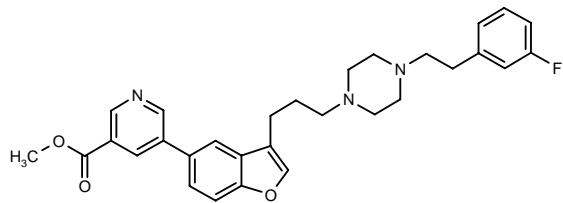
SOURCE – Merck Sharp & Dohme.

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1. Bourrain, S. et al. (Merck Sharp & Dohme, Ltd.) *Azetidine, pyrrolidine and piperidine derivs. as 5-HT_{1D} receptor agonists*. WO 9745426.

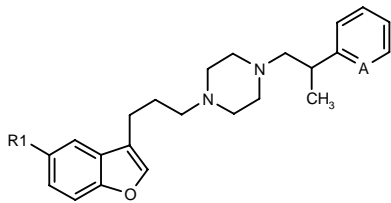
259868

5-[3-[3-[4-[2-(3-Fluorophenyl)ethyl]piperazin-1-yl]propyl]-benzofuran-5-yl]pyridine-3-carboxylic acid methyl ester



C30-H32-F-N3-O3; Mol wt: 501.60

ACTION – Antimigraine agent, a 5-HT receptor agonist with high affinity and selectivity for the 5-HT_{1D} (5-HT_{1Dα}) receptor subtype relative to the 5-HT_{1B} (5-HT_{1Dβ}) subtype, and thus expected to be associated with fewer side effects, particularly cardiovascular effects, compared to non-subtype-selective 5-HT_{1D} receptor agonists. Other specifically claimed piperazine, piperidine and tetrahydropyridine derivatives include the following:



Compound	R1	A	Formula
260643	3-Pyr	CH	C ₂₉ H ₃₃ N ₃ O
260644	5-(MeOCH ₂)-3-Pyr	CH	C ₃₁ H ₃₇ N ₃ O ₂
260645	3-Pyr	N	C ₂₈ H ₃₂ N ₄ O
260646	5-pyrimidinyl	CH	C ₂₈ H ₃₂ N ₄ O
260647	5-pyrimidinyl	N	C ₂₇ H ₃₁ N ₅ O
260648	4-Pyr	CH	C ₂₉ H ₃₃ N ₃ O
260649	6-MeO-3-Pyr	N	C ₂₉ H ₃₄ N ₄ O ₂
260650	2-oxo-1,2-dihydro-5-Pyr	N	C ₂₈ H ₃₂ N ₄ O ₂

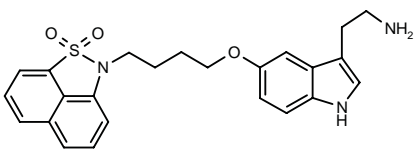
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Bourrain, S. et al. (Merck Sharp & Dohme, Ltd.) *Piperazine, piperidine and tetrahydropyridine derivs. as 5-HT receptor agonists*. WO 9745432.

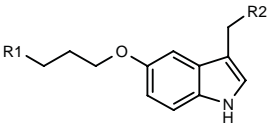
260062

N-[4-[3-(2-Aminoethyl)-1*H*-indol-5-yloxy]butyl]-1,8-naphthalenesultam



C24-H25-N3-O3-S; Mol wt: 435.54

ACTION – Antimigraine agent, a potent and selective 5-HT_{1D} receptor agonist (K_i = 0.68 nM against [³H]-5-HT binding vs. 5.3 nM for sumatriptan) with about 300-fold selectivity versus 5-HT_{1A} receptors (K_i = 206 nM) compared to 58-fold selectivity for sumatriptan (K_i = 307 nM). Other compounds from this series of 5-alkoxy-tryptamine derivatives include the following:



Compound	R1	R2	Formula
260896	t-BuOCONH	1-Me-2(S)-pyrrolidinyl	C ₂₂ H ₃₃ N ₃ O ₃
260897	NHCO2CH2Ph	1-Me-2(S)-pyrrolidinyl	C ₂₅ H ₃₁ N ₃ O ₃
260898	1,3-dioxo-2-isindolinyl	1-Me-2(S)-pyrrolidinyl	C ₂₅ H ₂₇ N ₃ O ₃
260899	1,3-dioxo-2-isindolinyl-CH2CH2	1-Me-2(S)-pyrrolidinyl	C ₂₇ H ₃₁ N ₃ O ₃
260900	1,3-dioxo-2-isindolinyl-CH2	1-Me-2(S)-pyrrolidinyl	C ₂₆ H ₂₉ N ₃ O ₃
260901	1,3-dioxo-2-isindolinyl	CH2NH2	C ₂₁ H ₂₁ N ₃ O ₃
260902	1,3-dioxo-2-isindolinyl-CH2	CH2NH2	C ₂₂ H ₂₃ N ₃ O ₃
260904	1,1-dioxo-2H-naphth-[1,8-cd]isothiazol-2-yl	CH2NH2	C ₂₃ H ₂₃ N ₃ O ₃ S
260905	(t-BuOCONH)2C=NCH2	1-Me-2(S)-pyrrolidinyl	C ₂₉ H ₄₅ N ₅ O ₅

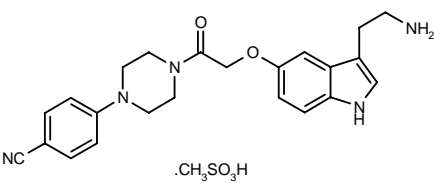
SOURCE – Allelix.

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260121

4-[4-[2-[3-(2-Aminoethyl)-1*H*-indol-5-yloxy]acetyl]piperazin-1-yl]benzonitrile methanesulfonate



C23-H25-N5-O2.C-H4-O3-S; Mol wt: 499.58

ACTION – Agent for the treatment of migraine, the mesylate salt of a known selective 5-HT_{1D/1B} receptor agonist. This salt exhibits greatly improved water solubility over other known salts of the compound and is thus suited for the preparation of solutions for oral or nasal administration.

SOURCE – Pierre Fabre.

REFERENCES

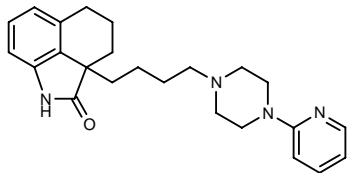
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

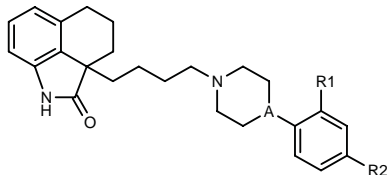
261154

2a-[4-[4-(2-Pyridyl)piperazin-1-yl]butyl]-1,2,2a,3,4,5-hexahydrobenz[cd]indol-2-one



C24-H30-N4-O; Mol wt: 390.53

ACTION – Agent for the treatment of CNS disorders with strong affinity and selectivity for 5-HT₇ receptors (K_i = 11 nM against [³H]-5-CT binding to cloned human 5-HT₇ receptors) over 5-HT₂ receptors (K_i = 120 nM against [³H]-ketanserin binding in rat cortical preparations). Within this series of hexahydrobenz[cd]indole derivatives, the following are also included:



Compound	R1	R2	A	Formula
261483	OMe	H	N	C ₂₆ H ₃₃ N ₃ O ₂
261484	H	OMe	CH	C ₂₇ H ₃₄ N ₂ O ₂

Such compounds may have potential in the treatment of sleep disorders, anxiety and depression.

SOURCE – Meiji Seika.

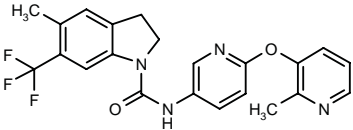
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ANXIOLYTICS

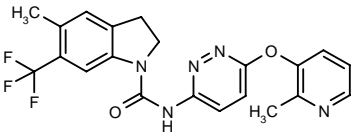
260132

5-Methyl-N-[6-(2-methylpyridin-3-yloxy)pyridin-3-yl]-6-(trifluoromethyl)indoline-1-carboxamide



C22-H19-F3-N4-O2; Mol wt: 428.41

ACTION – 5-HT_{2C} receptor antagonist for the treatment of CNS disorders such as anxiety and depression. Another specifically claimed indoline derivative is:



260926: C21-H18-F3-N5-O2

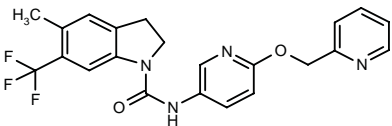
SOURCE – SmithKline Beecham.

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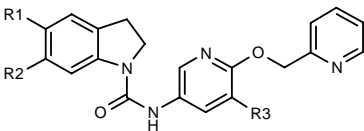
260133

5-Methyl-N-[6-(2-pyridylmethoxy)pyridin-3-yl]-6-(trifluoromethyl)indoline-1-carboxamide



C22-H19-F3-N4-O2; Mol wt: 428.41

ACTION – 5-HT_{2C} receptor antagonist with potential in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive–compulsive disorders, migraine, Alzheimer’s disease, sleep disorders, eating disorders, panic attacks, schizophrenia, drug and alcohol withdrawal symptoms, and disorders associated with spinal trauma and/or head injury. Other specifically claimed compounds from this series of indoline derivatives include the following:



Compound	R1	R2	R3	Formula
260942	CF3	H	H	C ₂₁ H ₁₇ F ₃ N ₄ O ₂
260943	Me	CF3	Me	C ₂₃ H ₂₁ F ₃ N ₄ O ₂
260944	Br	H	H	C ₂₀ H ₁₇ BrN ₄ O ₂
260945	H	CF3	H	C ₂₁ H ₁₇ F ₃ N ₄ O ₂

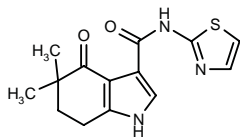
SOURCE – SmithKline Beecham.

REFERENCES

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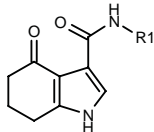
260764

5,5-Dimethyl-4-oxo-*N*-(2-thiazolyl)-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide



C14-H15-N3-O2-S; Mol wt: 289.35

ACTION – Agent that selectively binds to GABA_A brain receptors ($K_i = 2$ nM against [³H]-flumazenil binding using rat cortical tissue preparations), with potential in the treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory and alertness. A representative compound from a series of fused pyrrolo-carboxamides that are highly selective agonists, antagonists or inverse agonists at GABA_A brain receptors, wherein the following are also specifically claimed:



Compound	R1	Formula
261056	5-Me-2-thiazolyl	C ₁₃ H ₁₃ N ₃ O ₂ S
261057	2-quinoxaliny	C ₁₇ H ₁₄ N ₄ O ₂
261058	6-quinoxaliny	C ₁₇ H ₁₄ N ₄ O ₂

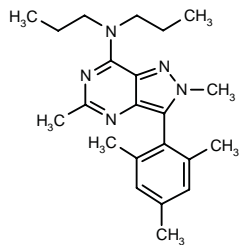
SOURCE – Neurogen.

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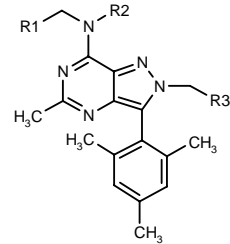
260767

N-[2,5-Dimethyl-3-(2,4,6-trimethylphenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]-*N,N*-dipropylamine

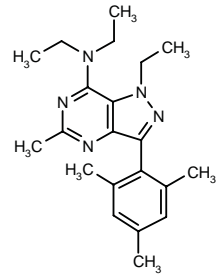


C22-H31-N5; Mol wt: 365.52

ACTION – Agent for the treatment of stress-related disorders such as posttraumatic stress disorder, depression, headache and anxiety that selectively binds to corticotropin-releasing factor (CRF) receptors ($IC_{50} = 1.4$ nM). Within this series of highly selective partial agonists or antagonists at human CRF₁ receptors, the following compounds are also specifically claimed:



Compound	R1	R2	R3	Formula
261065	Me	Et	Me	C ₂₁ H ₂₉ N ₅
261066	Et	cyclopropyl-CH2	H	C ₂₃ H ₃₁ N ₅
261067	Et	Et	H	C ₂₁ H ₂₉ N ₅
261068	Pr	Et	H	C ₂₂ H ₃₁ N ₅
261069	Me	Et	H	C ₂₀ H ₂₇ N ₅
261070	vinyl	allyl	H	C ₂₂ H ₂₇ N ₅
261071	Me	H	H	C ₁₈ H ₂₃ N ₅
261072	-CH2OCH2CH2-		H	C ₂₀ H ₂₅ N ₅ O
261073	Me	CH2Ph	H	C ₂₅ H ₂₉ N ₅
261074	CH2OMe	CH2CH2OMe	H	C ₂₂ H ₃₁ N ₅ O ₂



261075: C21-H29-N5

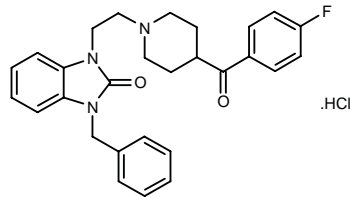
SOURCE – Neurogen.

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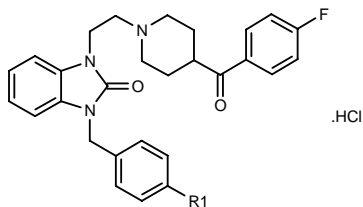
260848

1-Benzyl-3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-2,3-dihydro-1*H*-benzimidazol-2-one hydrochloride



C28-H28-F-N3-O2.HCl; Mol wt: 494.01

ACTION – Agent for the treatment of a variety of disorders including anxiety, depression, obesity, bulimia, hypertension, memory loss, sexual dysfunction, schizophrenia, gastrointestinal disorders, headache, Alzheimer’s disease and sleep disorders with affinity for 5-HT receptors such as 5-HT_{1D} and 5-HT_{2A} receptors. Within this series of 2,3-dihydro-1*H*-benzimidazol-2-one derivatives, the following are also included:



Compound	R1	Formula
261277	5-Me-1,2,4-oxadiazol-3-yl	C ₃₁ H ₃₀ FN ₅ O ₃ .HCl
261278	5-Me-1,3,4-oxadiazol-2-yl	C ₃₁ H ₃₀ FN ₅ O ₃ .HCl
261279	NH2	C ₂₈ H ₂₉ FN ₄ O ₂ .HCl

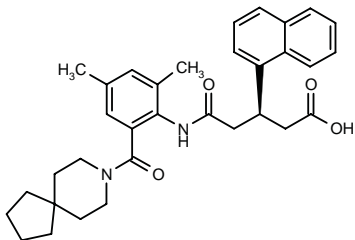
SOURCE – Lilly.

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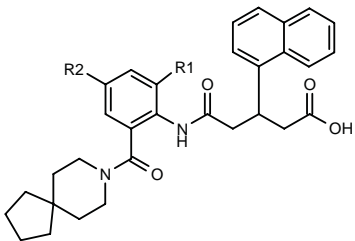
261157

N-[2-(8-Azaspiro[4.5]decan-8-ylcarbonyl)-4,6-dimethylphenyl]-3(*R*)-(1-naphthyl)glutaramic acid



C33-H38-N2-O4; Mol wt: 526.67

ACTION – Anxiolytic and gastric antisecretory agent, a selective antagonist of cholecystokinin CCK_B/gastrin receptors in the CNS (IC₅₀ = 5.1 nM against [³H]-[pBC264]-CCK-7 binding in guinea pig cortical membranes vs. 3.0 nM for pentagastrin) and in the gastrointestinal system (IC₅₀ = 4.3 nM for inhibition of the increase in cytosolic calcium induced by gastrin in rabbit gastric mucous membrane cells), with no affinity for CCK_A receptors (IC₅₀ > 1.0 μM). Anxiolytic activity was demonstrated in an elevated plus maze in rats, in which at a dose of 0.3 mg/kg i.p. it increased entries into and time spent in open arms by 31.5 and 50.9%, respectively, over control animals. Other compounds from this series of anthranilic acid diamides include the following:



Compound	R1	R2	Isomer	Formula
261401	Cl	Me	R	C ₃₂ H ₃₅ ClN ₂ O ₄
261402	Cl	Cl	R	C ₃₁ H ₃₂ Cl ₂ N ₂ O ₄
261403	Me	Me	S	C ₃₃ H ₃₈ N ₂ O ₄
261404	Cl	Me	S	C ₃₂ H ₃₅ ClN ₂ O ₄

SOURCE – Rotta Research.

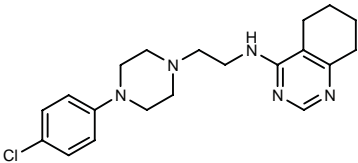
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ANTIPSYCHOTIC DRUGS

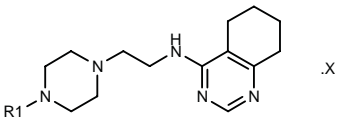
260103

N-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-*N*-(5,6,7,8-tetrahydroquinazolin-4-yl)amine



C20-H26-Cl-N5; Mol wt: 371.91

ACTION – Antipsychotic agent, a dopamine D₄ receptor antagonist (K_i = 0.01-1 nM) with selectivity over D₂ receptors (K_i > 5 nM), also shown to possess high affinity for 5-HT₂ and muscarinic M₁/M₂ receptors and α₁-adrenoceptors, with K_i values in the range 0.1-100 nM. Antipsychotic activity was demonstrated by its ability to antagonize methamphetamine-induced hyperactivity in mice (ED₅₀ = 1.0 mg/kg p.o.), while showing little cataleptogenic potential. No deaths were observed following p.o. administration of 50 mg/kg to rats. Other related fused heterocyclic compounds include the following:



Compound	R1	X	Formula
261700	2-pyrimidinyl	H2O	C ₁₈ H ₂₅ N ₇ .H ₂ O
261701	2-MeO-Ph		C ₂₁ H ₂₉ N ₅ O
261702	2-Cl-Ph		C ₂₀ H ₂₆ ClN ₅
261703	3-Cl-Ph		C ₂₀ H ₂₆ ClN ₅
261704	4-Br-Ph		C ₂₀ H ₂₆ BrN ₅
261705	Ph		C ₂₀ H ₂₇ N ₅

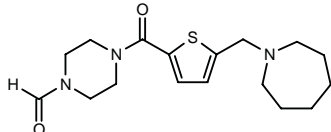
SOURCE – Yoshitomi.

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260538

4-[5-(Perhydroazepin-1-ylmethyl)thien-2-ylcarbonyl]-piperazine-1-carbaldehyde



C17-H25-N3-O2-S; Mol wt: 335.46

ACTION – Antipsychotic agent proven to antagonize phencyclidine (PCP) effects in rats.

SOURCE – Yamanouchi.

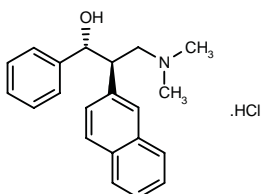
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ANTIDEPRESSANTS

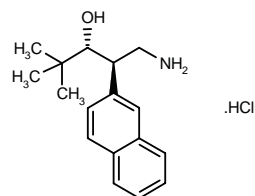
261127

(±)-(R*,R*)-3-(Dimethylamino)-2-(2-naphthyl)-1-phenylpropan-1-ol hydrochloride



C21-H23-N-O.HCl; Mol wt: 341.88

ACTION – Potent, broad-spectrum monoamine reuptake inhibitor that binds with high affinity to human transporters for 5-HT, norepinephrine and dopamine ($K_D = 5.59 \pm 0.02$, 44 ± 2 and 70 ± 8 nM, respectively, for competition with [3 H]-imipramine, [3 H]-nisoxetine and [3 H]-Win-35428 binding). It inhibited the reuptake of 5-HT, norepinephrine and dopamine in rat brain synaptosomes with K_i values of 4.1 ± 0.6 , 15 ± 2 and 12 ± 1 nM, respectively, whereas it displayed low affinity for the NMDA (PCP site) receptor ($IC_{50} = 143 \pm 16$ μ M for displacement of [3 H]-MK-801 binding in rat brain membranes). Potentially useful as an antidepressant. Another γ -amino alcohol with a different profile (comparable affinity for human 5-HT and norepinephrine transporters but little affinity for the human dopamine transporter; marked species selectivity for the rat dopamine transporter) is:



261128: C17-H23-N-O.HCl

SOURCES – Hong Kong Univ. Sci. Technol., Kowloon (HK); Mayo Clinic, Jacksonville, FL (US); Univ. Pittsburgh, Pittsburgh, PA (US).

REFERENCES

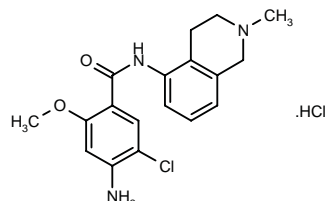
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

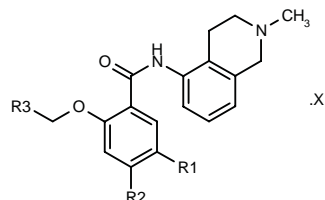
260123

4-Amino-5-chloro-2-methoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide hydrochloride



C18-H20-Cl-N3-O2.HCl; Mol wt: 382.29

ACTION – Anticonvulsant that binds to the same receptor as SB-204269 ($pK_i > 7$ against [3 H]-SB-204269 binding in rat forebrain tissue preparations), reported to be effective in the maximal electroshock test in mice at 30 mg/kg p.o. Also claimed for the treatment or prevention of anxiety, mania, depression, panic disorders, etc. Other compounds from this series of substituted benzamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
261015	Br	NH2	H		C ₁₈ H ₂₀ BrN ₃ O ₂
261016	Cl	NH2	Et		C ₂₀ H ₂₄ ClN ₃ O ₂
261017	Br	OMe	H		C ₁₉ H ₂₁ BrN ₃ O ₃
261018	Cl	Me	H		C ₁₉ H ₂₁ ClN ₃ O ₂
261019	Br	i-PrO	H	HCl	C ₂₁ H ₂₅ BrN ₃ O ₃ .HCl
261021	Cl	i-PrO	H	HCl	C ₂₁ H ₂₅ ClN ₃ O ₃ .HCl

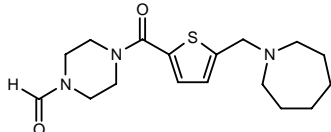
SOURCE – Yoshitomi.

REFERENCES

1. Kuroita, T. et al. (Yoshitomi Pharm. Ind., Ltd.) *Fused heterocyclic cpds. and medicinal uses thereof*. WO 9747601.

260538

4-[5-(Perhydroazepin-1-ylmethyl)thien-2-ylcarbonyl]-piperazine-1-carbaldehyde



C17-H25-N3-O2-S; Mol wt: 335.46

ACTION – Antipsychotic agent proven to antagonize phencyclidine (PCP) effects in rats.

SOURCE – Yamanouchi.

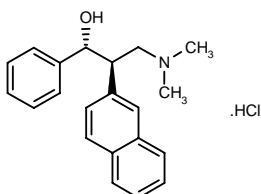
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1. Kimura, T. et al. (Yamanouchi Pharm. Co., Ltd.) *Novel thiophene derivs.* JP 98017564.

ANTIDEPRESSANTS

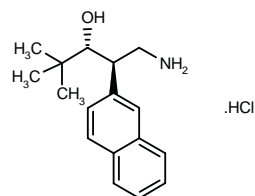
261127

(±)-(R*,R*)-3-(Dimethylamino)-2-(2-naphthyl)-1-phenylpropan-1-ol hydrochloride



C21-H23-N-O.HCl; Mol wt: 341.88

ACTION – Potent, broad-spectrum monoamine reuptake inhibitor that binds with high affinity to human transporters for 5-HT, norepinephrine and dopamine ($K_D = 5.59 \pm 0.02$, 44 ± 2 and 70 ± 8 nM, respectively, for competition with [3 H]-imipramine, [3 H]-nisoxetine and [3 H]-Win-35428 binding). It inhibited the reuptake of 5-HT, norepinephrine and dopamine in rat brain synaptosomes with K_i values of 4.1 ± 0.6 , 15 ± 2 and 12 ± 1 nM, respectively, whereas it displayed low affinity for the NMDA (PCP site) receptor ($IC_{50} = 143 \pm 16$ μ M for displacement of [3 H]-MK-801 binding in rat brain membranes). Potentially useful as an antidepressant. Another γ -amino alcohol with a different profile (comparable affinity for human 5-HT and norepinephrine transporters but little affinity for the human dopamine transporter; marked species selectivity for the rat dopamine transporter) is:



261128: C17-H23-N-O.HCl

SOURCES – Hong Kong Univ. Sci. Technol., Kowloon (HK); Mayo Clinic, Jacksonville, FL (US); Univ. Pittsburgh, Pittsburgh, PA (US).

REFERENCES

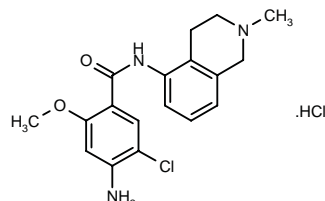
1. Carlier, P.R. et al. *Synthesis of a potent wide-spectrum serotonin-, norepinephrine-, dopamine-reuptake inhibitor (SNDRI) and a species-selective dopamine-reuptake inhibitor based on the γ -amino alcohol functional group*. Bioorg Med Chem Lett 1998, 8(5): 487.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

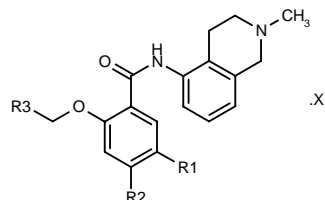
260123

4-Amino-5-chloro-2-methoxy-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)benzamide hydrochloride

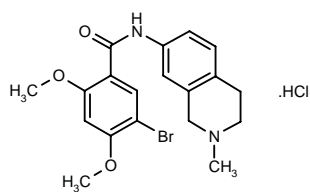


C18-H20-Cl-N3-O2.HCl; Mol wt: 382.29

ACTION – Anticonvulsant that binds to the same receptor as SB-204269 ($pK_i > 7$ against [3 H]-SB-204269 binding in rat forebrain tissue preparations), reported to be effective in the maximal electroshock test in mice at 30 mg/kg p.o. Also claimed for the treatment or prevention of anxiety, mania, depression, panic disorders, etc. Other compounds from this series of substituted benzamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
261015	Br	NH2	H		C ₁₈ H ₂₀ BrN ₃ O ₂
261016	Cl	NH2	Et		C ₂₀ H ₂₄ ClN ₃ O ₂
261017	Br	OMe	H		C ₁₉ H ₂₁ BrN ₃ O ₃
261018	Cl	Me	H		C ₁₉ H ₂₁ ClN ₃ O ₂
261019	Br	i-PrO	H	HCl	C ₂₁ H ₂₅ BrN ₃ O ₃ .HCl
261021	Cl	i-PrO	H	HCl	C ₂₁ H ₂₅ ClN ₃ O ₃ .HCl



261020: C19-H21-Br-N2-O3.HCl

SOURCE – SmithKline Beecham.

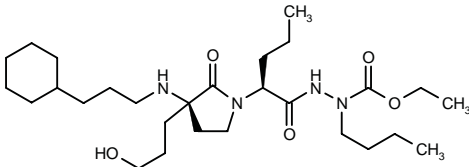
REFERENCES

1. Harling, J.D. (SmithKline Beecham plc) *Substd. benzamide derivs. and their use as anticonvulsants*. WO 9748683.

**THERAPY OF IMMUNOLOGICAL
NEUROMUSCULAR DISORDERS**

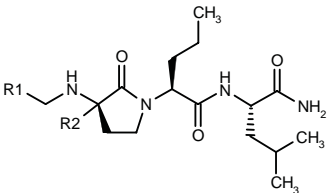
260485

2-Butyl-3-[2(*S*)-[3(*R*)-(3-cyclohexylpropylamino)-3-(3-hydroxypropyl)-2-oxopyrrolidin-1-yl]pentanoyl]carbamic acid ethyl ester

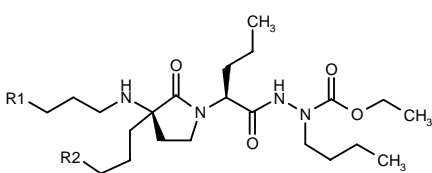


C28-H52-N4-O5; Mol wt: 524.74

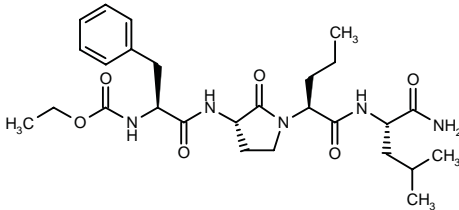
ACTION – Agent for the treatment of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, type I diabetes, lupus erythematosus, Graves’ disease and pemphigus that acts by inhibiting the binding of peptides to major histocompatibility complex (MHC) class II molecules. *In vitro*, compound was found to inhibit biotinylated rat myelin basic protein (RMBP) 90-102 binding to DR1 with IC₅₀ values of 0.16 μM when incubated for 20 min and 0.63 μM when incubated for 5 h. A representative compound from a series of pseudo-peptide lactams, wherein the following are also included:



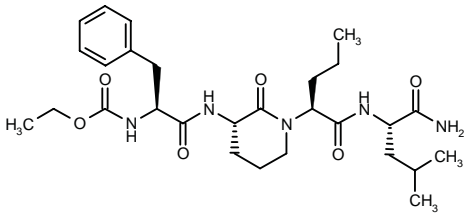
Compound	R1	R2	Formula
261085	cyclohexyl-C(Me)=CH	H	C ₂₅ H ₄₄ N ₄ O ₃
261088	cycloheptyl-CH ₂ CH ₂	H	C ₂₅ H ₄₆ N ₄ O ₃
261089	cyclohexyl-CH(Me)CH ₂	H	C ₂₅ H ₄₆ N ₄ O ₃
261090	cycloheptyl-CH ₂ CH ₂	Pr	C ₂₈ H ₅₂ N ₄ O ₃
261091	cyclohexyl-CH ₂ CH ₂	(CH ₂) ₃ OH	C ₂₇ H ₅₀ N ₄ O ₄
261093	1,2,3,4-tetrahydro-2-Naph	Pr	C ₂₉ H ₄₆ N ₄ O ₃



Compound	R1	R2	Formula
261092	cycloheptyl	H	C ₂₉ H ₅₄ N ₄ O ₄
261094	cyclohexyl	N3	C ₂₈ H ₅₁ N ₇ O ₄
261095	cyclohexyl	NH ₂	C ₂₈ H ₅₃ N ₅ O ₄
261096	cyclohexyl	NHC(=NH)NH ₂	C ₂₉ H ₅₅ N ₇ O ₄



261086: C27-H41-N5-O6



261087: C28-H43-N5-O6

SOURCE – Merck & Co.

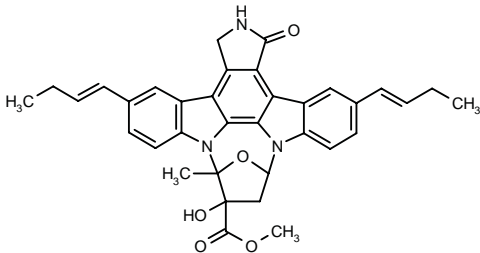
REFERENCES

1. Acton, J.J. III et al. (Merck & Co., Inc.) *Pseudopeptide lactam inhibitors of peptide binding to MHC class II proteins*. US 5719296.

COGNITION-ENHANCING DRUGS

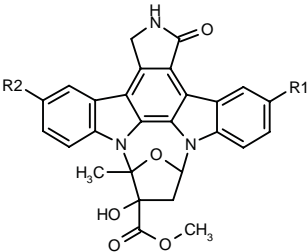
260074

5,16-Bis(1-butenyl)-9,12-epoxy-10-hydroxy-9-methyl-1-oxo-2,3,9,10,11,12-hexahydro-1*H*-diindolo-[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxylic acid methyl ester



C35-H33-N3-O5; Mol wt: 575.66

ACTION – Derivative of K-252a with potential in the treatment of neurological disorders such as Alzheimer’s disease, amyotrophic lateral sclerosis, Parkinson’s disease, stroke, ischemia, Huntington’s disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathies, head or spinal cord injury and disorders associated with excitatory amino acids that acts by enhancing the function and/or survival of trophic factor-responsive cells such as neurons. Compound was found to produce 291 and 290% increases in choline acetyltransferase (ChAT) activity, considered an enzymatic marker of a functional cholinergic neuron, in rat spinal cord and basal forebrain cultures at 300 and 250 nM, respectively. Other derivatives of K-252a include the following:



Compound	R1	R2	Formula
260993	CH=CHPh	H	C ₃₅ H ₂₇ N ₃ O ₅
260994	H	CH=CHCO ₂ Et	C ₃₂ H ₂₇ N ₃ O ₇
260995	H	2-Pyr-CH=CH	C ₃₄ H ₂₆ N ₄ O ₅
260997	H	2-Pyr-CH ₂ CH ₂	C ₃₄ H ₂₈ N ₄ O ₅
260998	NH ₂	2-Pyr-CH ₂ CH ₂	C ₃₄ H ₂₉ N ₅ O ₅
260999	CH ₂ CH ₂ SMe	CH ₂ CH ₂ SMe	C ₃₃ H ₃₃ N ₃ O ₅ S ₂

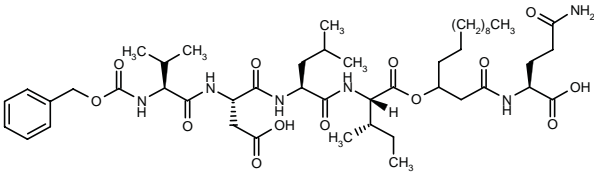
SOURCES – Cephalon; Kyowa Hakko.

REFERENCES

1. Hudkins, R.L. et al. (Cephalon, Inc.; Kyowa Hakko Kogyo Co., Ltd.) *Selected derivs. of K-252a*. WO 9746565.

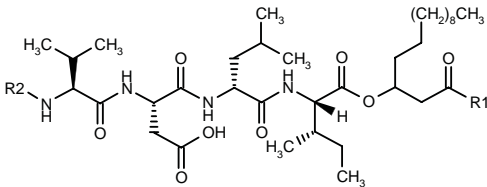
260203

N^α-[3-(Benzyloxycarbonyl-L-valyl-L-aspartyl-L-leucyl-L-isoleucyloxy)tetradecanoyl]-L-glutamine



C48-H78-N6-O13; Mol wt: 947.18

ACTION – Agent for the treatment of dementia and hyperlipidemia that acts by promoting the production of apolipoprotein E, as shown in HepG2 cells (665% increase at 10 μM relative to control = 100%). Other exemplified depsipeptides include the following:



Compound	R1	R2	Formula
261244	OH	t-BuOCO	C ₄₀ H ₇₂ N ₄ O ₁₁
261245	OH	H	C ₃₅ H ₆₄ N ₄ O ₉
261246	OH	t-BuOCO-D-Leu-	C ₄₆ H ₈₃ N ₅ O ₁₂
261247	OH	H-D-Leu-	C ₄₁ H ₇₅ N ₅ O ₁₀
261248	-Gln-Leu-OH	9-fluorenyl-CH ₂ OCO	C ₆₁ H ₉₃ N ₇ O ₁₄
261249	OH	9-fluorenyl-CH ₂ OCO	C ₅₀ H ₇₄ N ₄ O ₁₁

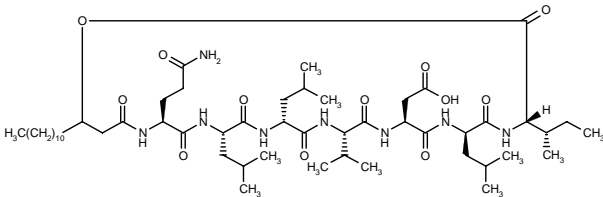
SOURCE – Nisshin Flour Milling.

REFERENCES

1. Yanai, M. et al. (Nisshin Flour Milling Co., Ltd.) *Depsipeptides and drugs containing the same as the active ingredient*. WO 9749722.

260204

3-Hydroxytetradecanoyl-L-glutaminy-L-leucyl-D-leucyl-L-valyl-L-aspartyl-D-leucyl-L-isoleucine C-1.8-O-3.1-lactone



C52-H92-N8-O12; Mol wt: 1021.35

ACTION – Cyclic depsipeptide that promotes the production of apolipoprotein E (457% at 1 μM relative to control = 100%) and apolipoprotein (147% at 1 μM relative to control = 100%), and inhibits the production of apolipoprotein B (43% at 1 μM relative to control = 100%). Claimed for use in the treatment of dementia, nerve injury and hyperlipidemia.

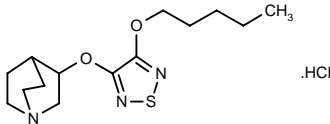
SOURCE – Nisshin Flour Milling.

REFERENCES

1. Yanai, M. et al. (Nisshin Flour Milling Co., Ltd.) *Cyclic depsipeptides and drugs containing the same as the active ingredient*. WO 9749724.

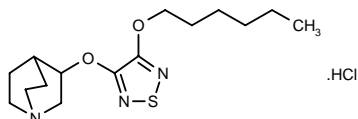
260579

(±)-3-[4-(Pentyloxy)-1,2,5-thiadiazol-3-yloxy]-1-azabicyclo[2.2.2]octane hydrochloride



C14-H23-N3-O2-S.HCl; Mol wt: 333.88

ACTION – Potent and selective muscarinic M_1 receptor agonist ($IC_{50} = 12.7$ and 47.7 nM for displacement of [3H]-oxotremorine-M and [3H]-pirenzepine binding in rat hippocampus membranes, respectively) proven to stimulate phosphoinositol hydrolysis in A9L cells transfected with the M_1 receptor ($EC_{50} = 164.8 \pm 30.5$ nM; efficacy = 47.5% [carbachol $100 \mu M = 100\%$]). No salivation was observed in mice after a dose of 10 mg/kg i.p., indicating a lack of M_3 receptor-agonist effects. Another compound from this series of 1,2,5-thiadiazole analogs of aceclidine is:



260580: C15-H25-N3-O2-S.HCl

Such compounds are potentially useful in the treatment of Alzheimer's disease, and further structure-activity studies are in progress in order to improve their potency, selectivity and efficacy.

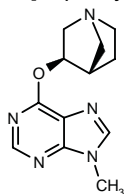
SOURCES – Lilly; Novo Nordisk.

REFERENCES

- Alt, C.A. et al. (Eli Lilly & Co.) *Heterocyclic cpds. and their preparation and use*. CA 2161176, EP 709381, JP 96225575.
- Bodick, N.C. et al. (Eli Lilly & Co.) *Method for treating anxiety*. EP 774256, WO 9717962.
- Mitch, C.H. and Shannon, H.E. (Eli Lilly & Co.) *Compsn. for treating pain*. WO 9720819.
- Ward, J.S. et al. *1,2,5-Thiadiazole analogues of aceclidine as potent m1 muscarinic agonists*. J Med Chem 1998, 41(3): 379.

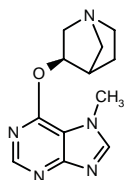
260765

exo-6-(1-Azabicyclo[2.2.1]hept-3-yloxy)-9-methylpurine

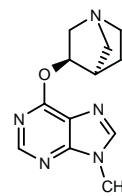


C12-H15-N5-O; Mol wt: 245.28

ACTION – Agent for the treatment of cognition disorders associated with decreased levels of acetylcholine such as Alzheimer's disease and Parkinson's disease, with central muscarinic receptor-agonist activity. Compound inhibited [3H]-QNB binding to human M_1 receptors expressed in CHO cells with a K_i value of $17.08 \mu M$. Other specifically claimed compounds from this series of 6-membered ring fused imidazoles include the following:



Compound	Isomer	Formula
261060	endo	C ₁₂ H ₁₅ N ₅ O
261061	exo	C ₁₂ H ₁₅ N ₅ O



261059: C12-H15-N5-O

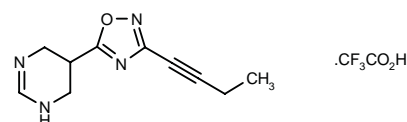
SOURCE – American Home Products.

REFERENCES

- Sabb, A.L. and Webb, M.B. (American Home Prods. Corp.) *6-Membered ring fused imidazoles as muscarinic agents*. US 5723468.

260962

5-[3-(1-Butynyl)-1,2,4-oxadiazol-5-yl]-1,4,5,6-tetrahydropyrimidine trifluoroacetate



C10-H12-N4-O.C2-H-F3-O2; Mol wt: 318.25

ACTION – Agent for the treatment of cognition disorders such as Alzheimer's disease with central muscarinic M_1 receptor-agonist activity, as demonstrated in binding studies ($IC_{50} = 16 \pm 6.9 \mu M$ for displacement of [3H]-QNB binding in rat brain membranes) and by stimulation of phosphoinositide turnover in rat cortex ($130 \pm 18\%$ at $100 \mu M$).

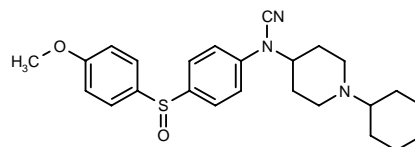
SOURCE – Univ. Toledo, Toledo, OH (US).

REFERENCES

- Messer, W.S. Jr. and Ojo, B. (Univ. Toledo) *Muscarinic agonists*. US 5726179.

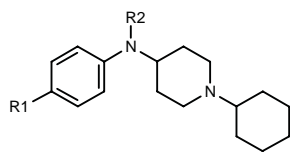
261199

N-(1-Cyclohexylpiperidin-4-yl)-N-[4-(4-methoxyphenyl)sulfinyl]phenyl]cyanamide



C25-H31-N3-O2-S; Mol wt: 437.60

ACTION – Agent for the treatment of cognitive and neurodegenerative disorders such as Alzheimer's disease, a muscarinic receptor antagonist with selectivity for M_2 receptors ($K_i = 9.0$ nM) over M_1 ($K_i = 189.0$ nM; M_1/M_2 ratio = 21) and M_4 receptors ($K_i = 39.3$ nM; M_4/M_2 ratio = 4.4). Also claimed for use in combination with an acetylcholinesterase inhibitor. Within this series of 1,4-disubstituted piperidines, the following are also included:



Compound	R1	R2	Formula
261736	OCH2Ph	CN	C ₂₅ H ₃₁ N ₃ O
261737	4-MeO-PhSO2	Me	C ₂₅ H ₃₄ N ₂ O ₃ S
261738	4-MeO-PhSO2	allyl	C ₂₇ H ₃₆ N ₂ O ₃ S
261739	1,3-benzodioxol-5-yl-SO2	CN	C ₂₅ H ₂₉ N ₃ O ₄ S
261740	cyclohexyl-SO2	CN	C ₂₄ H ₃₅ N ₃ O ₂ S
261741	4-(AcNH)-PhSO2	CN	C ₂₆ H ₃₂ N ₄ O ₃ S

SOURCE – Schering Corp.

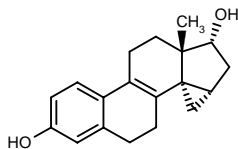
REFERENCES

1. Asberom, T. et al. (Schering Corp.) 1,4-Di-substd. piperidines as muscarinic antagonists. WO 9801425.

J-861

259662

14α,15α-Methyleneestra-1,3,5(10),8-tetraen-3,17α-diol
(14S,15β,17α)-3',15-Dihydrocycloprop[14,15]estra-1,3,5(10),8-tetraene-3,17-diol



C19-H22-O2; Mol wt: 282.38

ACTION – Estrogenic steroid with strong radical-scavenging properties (“scavestrogen”) and reduced effects on the genitals and mammary gland, proven to inhibit iron-induced lipid peroxidation (IC₅₀ = 1.51 ± 0.11 μM in brain synaptosomal membrane fractions), inhibit the formation of superoxide anion radicals in a xanthine/xanthine oxidase-induced luminescence reaction, exert iron-chelating effects and stimulate total antioxidative activity. Potentially useful as a nonfeminizing estrogen for the treatment of age-related cognitive dysfunction, neurodegenerative disorders, as well as atherogenesis and vascular pathology.

SOURCE – Jenapharm.

REFERENCES

1. Oettel, M. et al. (Jenapharm GmbH) Use of antioxidative steroids for the manufacture of pharmaceutical preparations for substitution therapy in man. DE 19524937, EP 753300, JP 97100292.

2. Schwarz, S. and Siemann, H.-J. (Jenapharm GmbH) 14α,15α-Methylenesteroids and process for their preparation. DE 4239945.

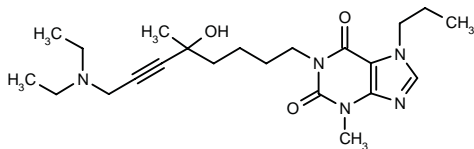
3. Oettel, M. The therapeutic potential for non-feminizing estrogens in men. Aging Male 1998, 1(Suppl, 1): Abst 008.

4. Römer, W. et al. Novel “scavestrogens” and their radical scavenging effects, iron-chelating, and total antioxidative activities: Δ^{8,9}-dehydro derivatives of 17α-estradiol and 17β-estradiol. Steroids 1997, 62(3): 304.

TREATMENT OF
CEREBROVASCULAR DISEASES

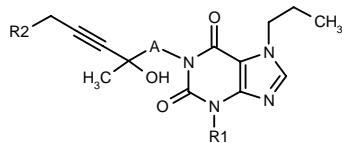
258724

1-[8-(Diethylamino)-5-hydroxy-5-methyl-6-octynyl]-3-methyl-7-propylxanthine



C22-H35-N5-O3; Mol wt: 417.55

ACTION – Neuroprotective and cerebral antiischemic agent proven active in a model of transient global ischemia in gerbils (31% protection of hippocampal CA1 neurons at 10 mg/kg i.p.) and in models of permanent focal cerebral ischemia in rats (56% reduction in infarct volume at 3 x 10 mg/kg i.p.) and mice (38% reduction in infarct volume at 10 mg/kg i.p.). Other specifically claimed xanthine derivatives include the following:



Compound	R1	R2	A	Formula
261374	Me	1-pyrrolidinyl	-(CH2)4-	C ₂₂ H ₃₃ N ₅ O ₃
261375	Bu	1-pyrrolidinyl	-(CH2)4-	C ₂₅ H ₃₉ N ₅ O ₃
261376	Pr	N(Et)2	-CH2-	C ₂₁ H ₃₃ N ₅ O ₃
261377	Et	N(Me)2	-(CH2)2-	C ₁₉ H ₂₉ N ₅ O ₃
261378	Et	N(Et)2	-(CH2)3-	C ₂₂ H ₃₅ N ₅ O ₃
261379	Me	4-Ac-1-Piz	-(CH2)4-	C ₂₄ H ₃₈ N ₆ O ₄
261380	Me	N(Et)2Me ⁺ I ⁻	-(CH2)4-	C ₂₃ H ₃₈ N ₅ O ₃

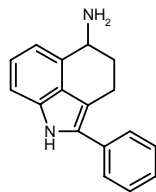
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Gebert, U. et al. (Hoechst AG) Xanthine derivs. with end-aminated alkynol side chains. EP 811623.

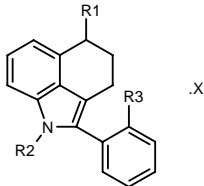
259898

2-Phenyl-1,3,4,5-tetrahydrobenz[d]indol-5-amine



C17-H16-N2; Mol wt: 248.33

ACTION – Neuroprotective agent, as demonstrated in neurons from fetal rat brain (51% inhibition of neuronal cell death at 1.0 µg/ml; IC₅₀ = 3.2 µg/ml for inhibition of veratrine-induced neuronal cell death) and in several animal models of cerebral ischemia. No mortality was observed following i.p. administration of 100 mg/kg to mice. Other related compounds include the following:



Compound	R1	R2	R3	X	Formula
261930	NH2	Me	H		C ₁₈ H ₁₈ N ₂
261931	NHMe	H	H		C ₁₈ H ₁₈ N ₂
261932	4-morpholinyl	Me	H	HCl	C ₂₂ H ₂₄ N ₂ O.HCl
261933	4-morpholinyl	H	F	HCl	C ₂₁ H ₂₁ FN ₂ O.HCl

Some compounds within the scope of the invention are also reported to possess analgesic activity.

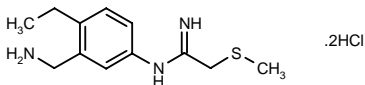
SOURCE – Mochida.

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1. Yamamoto, I. et al. (Mochida Pharm. Co., Ltd.) *Nerve cell protective agents*. WO 9745410.

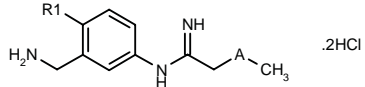
260057

N-[3-(Aminomethyl)-4-ethylphenyl]-2-(methylsulfanyl)-acetamidine dihydrochloride



C12-H19-N3-S.2HCl; Mol wt: 310.28

ACTION – Agent for the treatment of cerebrovascular disorders, an inhibitor of nitric oxide synthase (NOS) with selectivity for the neuronal isoform (nNOS; IC₅₀ = 6.3 nM) over the endothelial isoform (eNOS; IC₅₀ = 4519.7 nM). Other compounds from this series of substituted benzenes include the following:



Compound	R1	A	Formula
261934	OMe	S	C ₁₁ H ₁₇ N ₃ OS.2HCl
261935	Cl	S	C ₁₀ H ₁₄ ClN ₃ S.2HCl
261936	Et	O	C ₁₂ H ₁₉ N ₃ O.2HCl
261937	OMe	CH2	C ₁₂ H ₁₉ N ₃ O.2HCl
261938	Cl	CH2	C ₁₁ H ₁₆ ClN ₃ .2HCl

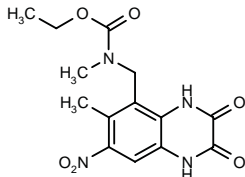
SOURCE – Chugai.

REFERENCES

1. Emura, T. et al. (Chugai Pharm. Co., Ltd.) *Substd. benzenes having NOS inhibitory effects*. WO 9746515.

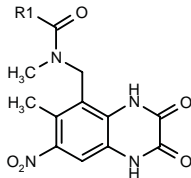
260065

N-Methyl-N-(6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)carbamic acid ethyl ester



C14-H16-N4-O6; Mol wt: 336.30

ACTION – Neuroprotective agent, an excitatory amino acid receptor antagonist that acts at NMDA (glycine site), AMPA and kainate receptors (IC₅₀ = 0.10, 0.21 and 0.29 µM, respectively). *In vivo* activity was demonstrated in the maximal electroshock assay in mice, where it gave 60% protection at 30 min after a dose of 10 mg/kg i.v., without ataxia. Other specifically claimed compounds from this series of quinoxaline-2,3-dione derivatives include the following:



Compound	R1	Formula
261257	2-thienyl	C ₁₆ H ₁₄ N ₄ O ₅ S
261258	2-furyl	C ₁₆ H ₁₄ N ₄ O ₆

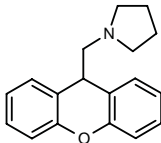
SOURCE – Warner-Lambert.

REFERENCES

1. Nikam, S.S. (Warner-Lambert Co.) *Amide derivs. of substd. quinoxaline 2,3-diones as glutamate receptor antagonists*. WO 9746539.

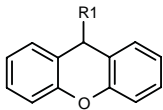
260067

1-(Xanthen-9-ylmethyl)pyrrolidine



C18-H19-N-O; Mol wt: 265.35

ACTION – Neuroprotective agent for the treatment of neurodegenerative disorders such as cerebral ischemia, Alzheimer’s disease, Huntington’s disease and Parkinson’s disease. At low s.c. or p.o. doses, it is reported to be associated with a marked protective effect against apoptotic cytolysis in newborn rat facial motor neurons, against kainic acid-induced cytolysis in rat hippocampal pyramidal cells, and against MPTP-induced cytolysis in mouse nigral neurons. Other specifically claimed xanthene derivatives include the following:



Compound	R1	Formula
260768	4-morpholinyl-CO	C ₁₈ H ₁₇ NO ₃
260769	4-morpholinyl-CH2	C ₁₈ H ₁₉ NO ₂
260770	ethynyl-CH2NHCO	C ₁₇ H ₁₃ NO ₂
260771	ethynyl-CH2NHCH2	C ₁₇ H ₁₅ NO
260772	ethynyl-CH2N(Me)CO	C ₁₈ H ₁₅ NO ₂
260773	ethynyl-CH2N(Me)CH2	C ₁₈ H ₁₇ NO
260774	CON(Me)CH2CN	C ₁₇ H ₁₄ N ₂ O ₂
260775	CH2N(Me)CH2CN	C ₁₇ H ₁₆ N ₂ O
260776	1-pyrrolidinyl-CS	C ₁₈ H ₁₇ NOS
260777	1,2,3,6-tetrahydro-1-Pyr-CO	C ₁₉ H ₁₇ NO ₂
260778	1,2,3,6-tetrahydro-1-Pyr-CH2	C ₁₉ H ₁₉ NO
260779	2,5-dihydro-1-pyrrolyl-CO	C ₁₈ H ₁₅ NO ₂
260780	2,5-dihydro-1-pyrrolyl-CH2	C ₁₈ H ₁₇ NO
260781	1-pyrrolyl-CH2	C ₁₈ H ₁₅ NO

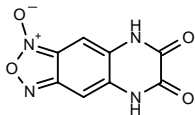
SOURCE – Novartis.

REFERENCES

1. Roggo, S. et al. (Novartis AG) *Anti-neurodegeneratively effective xanthene derivs.* WO 9746549.

260481

[1,2,5]Oxadiazolo[3,4-g]quinoxaline-6,7(5*H*,8*H*)-dione 1-oxide



C8-H4-N4-O4; Mol wt: 220.14

ACTION – Neuroprotective agent with AMPA receptor-antagonist activity (IC₅₀ = 7.6 μM against [³H]-AMPA binding in rat forebrain membranes).

SOURCE – American Home Products.

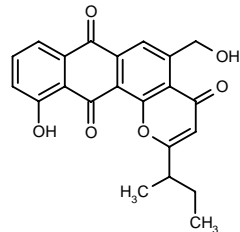
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1. Baudy, R.B. and Sulkowski, T.S. (American Home Prods. Corp.) *5*H*,8*H*-2-Oxa-1,3,5,8-tetraaza-cyclopenta[*b*]-naphthalene-6,7-diones.* US 5719153.

Cu39

258449

11-Hydroxy-5-(hydroxymethyl)-2-(1-methylpropyl)-7,12-dihydro-4*H*-anthra[1,2-*b*]pyran-4,7,12-trione



C22-H18-O6; Mol wt: 378.38

ACTION – Neuroprotective agent isolated from *Streptomyces* sp. cu39 (FERM BP-5482), found to protect N-18-RE-105 cells against toxicity caused by glutamate with an ED₅₀ value of 40 nM.

SOURCE – Kirin Brewery.

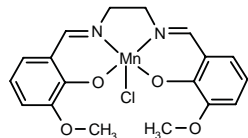
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1. Seto, H. and Shinya, K. (Kirin Brewery Co., Ltd.) *cu39, a neuroprotective substance, preparation method thereof and its use.* JP 97295976.

EUK-134

244570

(*SP*-5-13)-Chloro[2,2'-[1,2-ethanediylbis[(nitrilo-κ*N*)methylidyne]]bis[6-methoxyphenolato-κ*O*¹]]manganese



C18-H18-Cl-Mn-N2-O4; Mol wt: 416.74

ACTION – Neuroprotective agent, a salen–manganese complex that acts as a combined catalase/superoxide dismutase mimetic, proven effective in a rat focal cerebral ischemia model at doses of 0.25 and 2.5 mg/kg i.v. 3 h after middle cerebral artery occlusion (infarct volume reductions of approx. 90% at the highest dose), a significant effect being observed for up 72 h after occlusion. EUK-134 also exhibited cytoprotective activity against glucose- and glucose oxidase-induced cytotoxicity in human fibroblasts.

SOURCE – Eukarion.

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1. Malfroy-Camine, B. and Doctrow, S.R. (Eukarion., Inc.) *Synthetic catalytic free radical scavengers useful as antioxidants for prevention and therapy of disease.* US 5696109, WO 9640148, WO 9640149.

2. Baker, K. et al. *Synthetic combined superoxide dismutase/catalase mimetics are protective as a delayed treatment in a rat stroke model: A key role for reactive oxygen species in ischemic brain injury.* J Pharmacol Exp Ther 1998, 284(1): 215.

3. Fonck, C. et al. *In vitro and in vivo prevention of MPTP induced neurotoxicity by a synthetic superoxide scavenger, EUK-134.* Soc Neurosci Abst 1995, 21(Part 2): Abst 491.15.

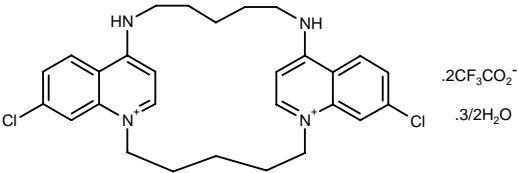
4. Gianello, P. et al. *EUK-134, a synthetic superoxide dismutase and catalase mimetic, protects rat kidneys from ischemia-reperfusion-induced damage*. Transplantation 1996, 62(11): 1664.

5. *EUK-134 effective in animal model of stroke*. Prous Science Daily Essentials January 28, 1998.

MISCELLANEOUS NEUROLOGIC
DRUGS

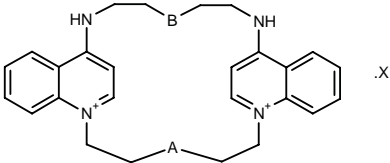
260136

1,1'-(Pentane-1,5-diyl)-*N,N'*-(pentane-1,5-diyl)bis(4-amino-7-chloroquinolinium) bistrifluoroacetate sesquihydrate

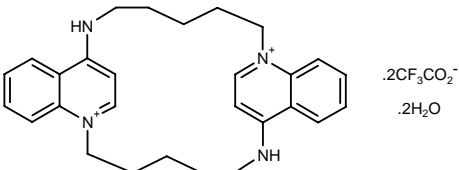


C32-H32-Cl2-F6-N4-O4.3/2H2-O; Mol wt: 748.55

ACTION – Calcium-activated potassium channel blocker, particularly the SK_{Ca} channel, as demonstrated by measuring its ability to inhibit the afterhyperpolarization of cultured rat sympathetic neurons (IC₅₀ = 3.1 ± 0.3 nM). Potentially useful in the treatment of myotonic muscular dystrophy, gastrointestinal motility disorders, memory disorders, narcolepsy and associated disorders, cancer, ethanol-induced neurotoxicity and bacterial infections. Within this series of bisquinolinium derivatives, the following are also included:



Compound	A	B	X	Formula
261022	O	O	2Br ⁻ .2H ₂ O	C ₂₆ H ₃₀ Br ₂ N ₄ O ₂ .2H ₂ O
261023	O	CH ₂	2Br ⁻ .2H ₂ O	C ₂₇ H ₃₂ Br ₂ N ₄ O.2H ₂ O
261024	S	CH ₂	2CF ₃ CO ₂ ⁻ .H ₂ O	C ₃₁ H ₃₂ F ₆ N ₄ O ₄ S.H ₂ O



261025: C32-H34-F6-N4-O4.2H2-O

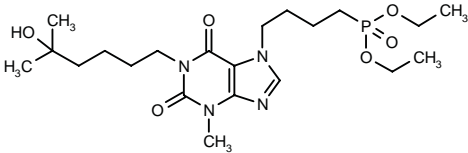
SOURCE – Univ. Coll. London, London (GB).

REFERENCES

1. Campos-Rosa, J. et al. (Univ. Coll. London) *Potassium channel blockers*. WO 9748705.

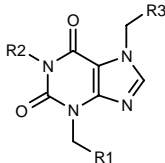
261289

4-[1-(5-Hydroxy-5-methylhexyl)-3-methylxanthin-7-yl]-butylphosphonic acid diethyl ester



C21-H37-N4-O6-P; Mol wt: 472.52

ACTION – Agent for reducing the loss of muscle function occurring in many disorders, as shown in an *in vivo* assay in immobilized rats. Compound is also reported to lower lipopolysaccharide (LPS)-induced mortality, antagonize the effects of substance P, LTD₄ and PAF and inhibit phosphodiesterases. Claimed for use in the treatment of muscular atrophy, muscular dystrophy and inflammatory bowel disease. Within this series of xanthine phosphonates and phosphine oxides, the following are also included:



Compound	R1	R2	R3	Formula
261366	H	H	CH ₂ CH ₂ PO(OEt) ₂	C ₁₃ H ₂₁ N ₄ O ₅ P
261367	Pr	Bu	(CH ₂) ₄ PO(OEt) ₂	C ₂₂ H ₃₉ N ₄ O ₅ P
261368	H	Pr	(CH ₂) ₃ PO(OEt) ₂	C ₁₇ H ₂₉ N ₄ O ₅ P
261369	H	(CH ₂) ₅ PO(OEt) ₂	Et	C ₁₈ H ₃₁ N ₄ O ₅ P
261370	H	(CH ₂) ₄ PO(OEt) ₂	Me	C ₁₆ H ₂₇ N ₄ O ₅ P
261371	H	(CH ₂) ₃ PO(OEt) ₂	Me	C ₁₅ H ₂₅ N ₄ O ₅ P
261372	H	(CH ₂) ₃ PO(OEt) ₂	cyclopropyl	C ₁₇ H ₂₇ N ₄ O ₅ P
261373	Me	(CH ₂) ₅ PO(OEt) ₂	Et	C ₁₉ H ₃₃ N ₄ O ₅ P

SOURCE – Hoechst Marion Roussel.

REFERENCES

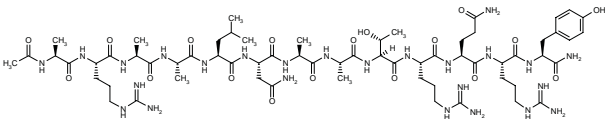
1. Billen, G. et al. (Hoechst AG) *Alkylxanthine phosphonates and alkylxanthine phosphine oxides and their use as pharmaceuticals*. US 5728686.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

260079

Acetyl-alanyl-arginyl-alanyl-alanyl-leucyl-asparaginyl-alanyl-alanyl-threonyl-arginyl-glutaminy-arginyl-tyrosinamide



C63-H107-N25-O18; Mol wt: 1502.70

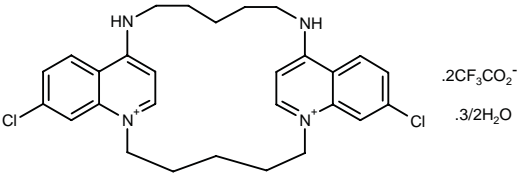
4. Gianello, P. et al. *EUK-134, a synthetic superoxide dismutase and catalase mimetic, protects rat kidneys from ischemia-reperfusion-induced damage*. Transplantation 1996, 62(11): 1664.

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MISCELLANEOUS NEUROLOGIC DRUGS

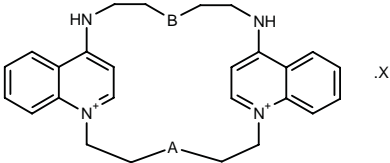
260136

1,1'-(Pentane-1,5-diyl)-*N,N'*-(pentane-1,5-diyl)bis(4-amino-7-chloroquinolinium) bistrifluoroacetate sesquihydrate

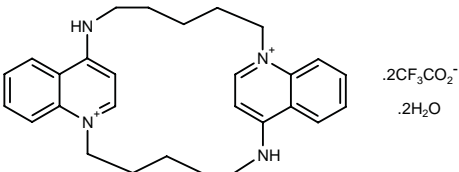


C32-H32-Cl2-F6-N4-O4.3/2H2-O; Mol wt: 748.55

ACTION – Calcium-activated potassium channel blocker, particularly the SK_{Ca} channel, as demonstrated by measuring its ability to inhibit the afterhyperpolarization of cultured rat sympathetic neurons (IC₅₀ = 3.1 ± 0.3 nM). Potentially useful in the treatment of myotonic muscular dystrophy, gastrointestinal motility disorders, memory disorders, narcolepsy and associated disorders, cancer, ethanol-induced neurotoxicity and bacterial infections. Within this series of bisquinolinium derivatives, the following are also included:



Compound	A	B	X	Formula
261022	O	O	2Br ⁻ .2H2O	C ₂₆ H ₃₀ Br ₂ N ₄ O ₂ .2H ₂ O
261023	O	CH2	2Br ⁻ .2H2O	C ₂₇ H ₃₂ Br ₂ N ₄ O.2H ₂ O
261024	S	CH2	2CF ₃ CO ₂ ⁻ .H2O	C ₃₁ H ₃₂ F ₆ N ₄ O ₄ S.H ₂ O



261025: C32-H34-F6-N4-O4.2H2-O

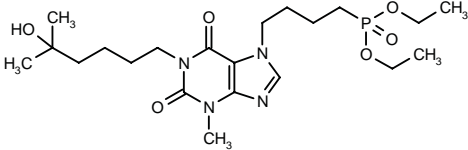
SOURCE – Univ. Coll. London, London (GB).

REFERENCES

1. Campos-Rosa, J. et al. (Univ. Coll. London) *Potassium channel blockers*. WO 9748705.

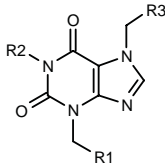
261289

4-[1-(5-Hydroxy-5-methylhexyl)-3-methylxanthin-7-yl]-butylphosphonic acid diethyl ester



C21-H37-N4-O6-P; Mol wt: 472.52

ACTION – Agent for reducing the loss of muscle function occurring in many disorders, as shown in an *in vivo* assay in immobilized rats. Compound is also reported to lower lipopolysaccharide (LPS)-induced mortality, antagonize the effects of substance P, LTD₄ and PAF and inhibit phosphodiesterases. Claimed for use in the treatment of muscular atrophy, muscular dystrophy and inflammatory bowel disease. Within this series of xanthine phosphonates and phosphine oxides, the following are also included:



Compound	R1	R2	R3	Formula
261366	H	H	CH2CH2PO(OEt)2	C ₁₃ H ₂₁ N ₄ O ₅ P
261367	Pr	Bu	(CH2)4PO(OEt)2	C ₂₂ H ₃₉ N ₄ O ₅ P
261368	H	Pr	(CH2)3PO(OEt)2	C ₁₇ H ₂₉ N ₄ O ₅ P
261369	H	(CH2)5PO(OEt)2	Et	C ₁₈ H ₃₁ N ₄ O ₅ P
261370	H	(CH2)4PO(OEt)2	Me	C ₁₆ H ₂₇ N ₄ O ₅ P
261371	H	(CH2)3PO(OEt)2	Me	C ₁₅ H ₂₅ N ₄ O ₅ P
261372	H	(CH2)3PO(OEt)2	cyclopropyl	C ₁₇ H ₂₇ N ₄ O ₅ P
261373	Me	(CH2)5PO(OEt)2	Et	C ₁₉ H ₃₃ N ₄ O ₅ P

SOURCE – Hoechst Marion Roussel.

REFERENCES

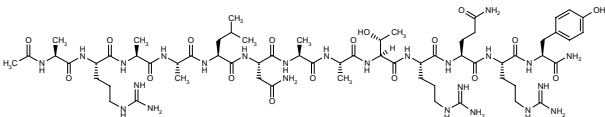
1. Billen, G. et al. (Hoechst AG) *Alkylxanthine phosphonates and alkylxanthine phosphine oxides and their use as pharmaceuticals*. US 5728686.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

260079

Acetyl-alanyl-arginyl-alanyl-alanyl-leucyl-asparaginyl-alanyl-alanyl-threonyl-arginyl-glutaminy-arginyl-tyrosinamide



C63-H107-N25-O18; Mol wt: 1502.70

ACTION – Selective neuropeptide Y (NPY) Y_2 -like receptor agonist derived from the NPY 24-36 amino acid sequence, with potential in the treatment of rhinitis, respiratory disorders, vasoconstriction predisposing to acute renal failure, cardiovascular disorders, inflammation and CNS disorders, particularly for the relief of nasal congestion administered nasally. In a binding assay, it gave IC_{50} values of 3.16 and > 1000 nM, respectively, against [125 I]-NPY binding to human Y_2 and Y_1 receptors. *In vivo*, it potently inhibited the reduction in heart rate produced by electrical stimulation of the vagal nerve in rats (Y_2 -mediated) while showing no pressor activity (Y_1 -mediated).

SOURCES – CRC Biopharm. Res.; Peptech.

REFERENCES

1. Potter, E. (Peptech, Ltd.; CRC Biopharm. Res., Ltd.) *Neuropeptide Y agonists*. WO 9746579.

MIZOLASTINE

Rec INN; BAN

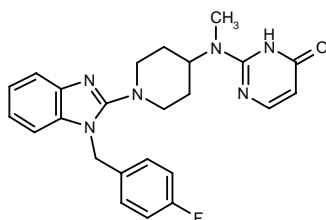
134006

2-[N-[1-[1-(4-Fluorobenzyl)-1H-benzimidazol-2-yl]-4-piperidinyl]-N-methylamino]pyrimidin-4(3H)-one

1-(4-Fluorobenzyl)-2-[4-[N-(3,4-dihydro-4-oxopyrimidin-2-yl)-N-methylamino]piperidin-1-yl]benzimidazole

MKC-431

SL-85.0324⁺



C24-H25-F-N6-O; Mol wt: 432.50

ACTION – Long-acting histamine H_1 receptor antagonist.

INDICATION – Symptomatic relief of seasonal or perennial allergic rhinoconjunctivitis and urticaria.

PRESENTATION – Tablets, 10 mg.

PROPRIETARY NAME – Mizollen (CH, DE, GB).

SOURCE – Synthelabo.

RECENT REFERENCES

1. Benavides, J. et al. *In vivo and in vitro interaction of the novel selective histamine H1 receptor antagonist mizolastine with H1 receptors in the rodent*. *Arzneim-Forsch-Drug Res* 1995, 45(5): 551.

2. Brostoff, J. et al. *Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria*. *Allergy* 1996, 51(5): 320.

3. Chaufour, S. et al. *Mizolastine, a new non-sedative H1 antagonist is devoid of CNS effects. A review of human pharmacology data*. *Allergy* 1996, 51(Suppl. 31): Abst P 517.

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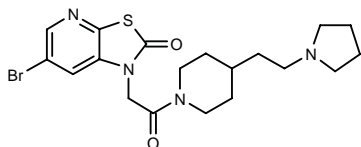
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ASTHMA THERAPY

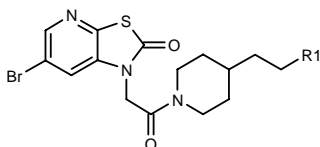
259003

6-Bromo-1-[2-oxo-2-[4-[2-(1-pyrrolidinyl)ethyl]piperidin-1-yl]ethyl]thiazolo[5,4-*b*]pyridin-2(1*H*)-one



C19-H25-Br-N4-O2-S; Mol wt: 453.40

ACTION – Antiasthmatic agent with a direct bronchospasmolytic action, as evidenced by inhibition of spontaneous tonus ($EC_{50} = 1.3 \mu M$) and contractions elicited by barium chloride in isolated guinea pig tracheal ring preparations ($EC_{50} = 4.1 \mu M$). *In vivo* efficacy was demonstrated by 93.1% inhibition of PAF-induced bronchoconstriction at a dose of 3 mg/kg i.v. in guinea pigs. Compound also inhibited guinea pig bronchial hyperreactivity elicited by PAF, substance P or bradykinin, with about 88, 76 and 90% inhibition, respectively, at a dose of 6 mg/kg i.v. Marked activity was also demonstrated in a series of conventional *in vivo* models including those designed to evaluate inhibition of protein extravasation or bronchospasm induced by mediator release from immunocompetent cells or the release of neuropeptides from C-fibers. A representative compound within a series of specifically claimed thiazolopyridines, wherein the following are also included:



Compound	R1	Formula
260364	N(Me)2	C ₁₇ H ₂₃ BrN ₄ O ₂ S
260365	CH ₂ N(Me)2	C ₁₈ H ₂₅ BrN ₄ O ₂ S

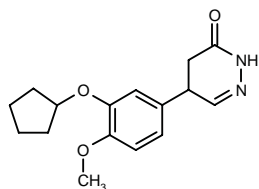
SOURCE – Klinge Pharma.

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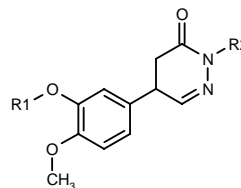
260106

5-(3-Cyclopentyloxy-4-methoxyphenyl)-2,3,4,5-tetrahydropyridazin-3-one



C16-H20-N2-O3; Mol wt: 288.35

ACTION – Agent for the treatment of inflammatory, allergic and autoimmune diseases such as asthma, dermatitis and rheumatoid arthritis, an inhibitor of phosphodiesterase type IV (PDE IV; $IC_{50} = 0.42 \mu M$ against enzyme from rat neutrophils). Compound was found to inhibit superoxide generation from rat neutrophils with an IC_{50} value of 30 nM. *In vivo*, it inhibited antigen-induced bronchoconstriction in sensitized guinea pigs ($ED_{50} = 0.4 \text{ mg/kg i.v.}$). Other compounds from this series of 5-phenyl-3-pyridazinone derivatives include the following:



Compound	R1	R2	Formula
261233	cyclopentyl	CH ₂ Ph	C ₂₃ H ₂₆ N ₂ O ₃
261234	cyclopropyl-CH ₂	H	C ₁₅ H ₁₈ N ₂ O ₃
261235	1-Me-cyclopropyl-CH ₂	H	C ₁₆ H ₂₀ N ₂ O ₃
261236	cyclopropyl-CH ₂	Me	C ₁₆ H ₂₀ N ₂ O ₃
261237	i-Bu	Me	C ₁₆ H ₂₂ N ₂ O ₃
261238	Bu	Me	C ₁₆ H ₂₂ N ₂ O ₃

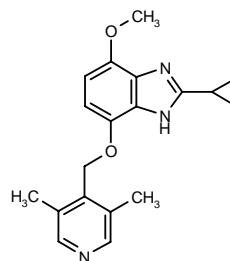
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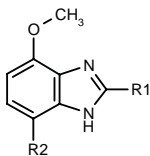
260131

2-Cyclopropyl-7-(3,5-dimethylpyridin-4-ylmethoxy)-4-methoxy-1*H*-benzimidazole



C19-H21-N3-O2; Mol wt: 323.39

ACTION – An inhibitor of cyclic AMP phosphodiesterase (cAMP-PDE), particularly type IV PDE, and of the production of tumor necrosis factor (TNF) with potential in the treatment of inflammatory and autoimmune diseases such as asthma, arthritis and septic shock. Other specifically claimed substituted azabicyclic compounds include the following:



Compound	R1	R2	Formula
260966	CH2OMe	3,5-(Cl)2-4-Pyr-NHCO	C ₁₆ H ₁₄ Cl ₂ N ₄ O ₃
260967	OMe	3,5-(Cl)2-4-Pyr-NHCO	C ₁₅ H ₁₂ Cl ₂ N ₄ O ₃
260968	cyclopropyl	3,5-(Cl)2-4-Pyr-NHCO	C ₁₇ H ₁₄ Cl ₂ N ₄ O ₂
260969	i-Pr	3,5-(Cl)2-4-Pyr-NHCO	C ₁₇ H ₁₆ Cl ₂ N ₄ O ₂
260970	cyclopropyl	3,5-(Me)2-4-isoxazolyl-NHCO	C ₁₇ H ₁₈ N ₄ O ₃
260971	CH2OMe	3,5-(Me)2-4-isoxazolyl-NHCO	C ₁₈ H ₁₈ N ₄ O ₄
260972	CH2OMe	3,5-(Me)2-4-Pyr-CH2O	C ₁₈ H ₂₁ N ₃ O ₃

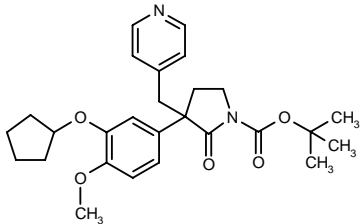
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260762

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-oxo-3-(pyridin-4-ylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester



C27-H34-N2-O5; Mol wt: 466.58

White solid, m.p. 148-9 °C.

ACTION – A potent inhibitor of phosphodiesterase type IV (PDE IV; IC₅₀ = 6.3 nM; K_i = 7.5 nM for displacement of rolipram binding) from a series of spirocyclic γ-lactams.

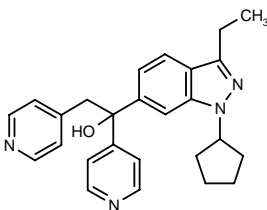
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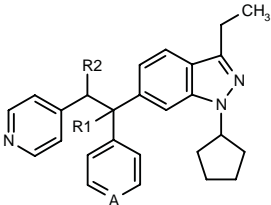
260849

1-(1-(Cyclopentyl-3-ethyl-1*H*-indazol-6-yl)-1,2-bis(4-pyridyl)ethanol



C26-H28-N4-O; Mol wt: 412.53

ACTION – An inhibitor of phosphodiesterase type IV (PDE IV) and of the production of tumor necrosis factor (TNF), with potential in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, CNS disorders such as depression and multiinfarct dementia, AIDS and septic shock. Other specifically claimed compounds from this series of substituted indazole derivatives include the following:



Compound	R1	R2	A	Formula
261280	bond		N	C ₂₆ H ₂₆ N ₄
261281	H	H	N	C ₂₆ H ₂₈ N ₄
261282	OH	H	N	C ₂₇ H ₂₉ N ₃ O
261283	bond		CH	C ₂₇ H ₂₇ N ₃
261284	H	H	CH	C ₂₇ H ₂₉ N ₃

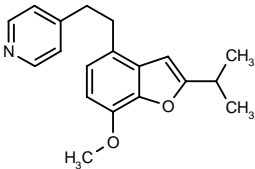
SOURCE – Pfizer.

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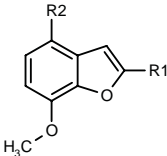
260876

2-Isopropyl-7-methoxy-4-[2-(4-pyridyl)ethyl]benzofuran



C19-H21-N-O2; Mol wt: 295.38

ACTION – A selective inhibitor of cyclic AMP phosphodiesterase, particularly type IV (PDE IV; -logIC₅₀ = 8.22), reported to possess low toxicity and high bioavailability. Claimed for use in the treatment of respiratory disorders such as asthma and dermatoses. Within this series of 4-substituted benzofurans, the following are also included:



Compound	R1	R2	Formula
261454	cyclopentyl-O	4-Pyr-CH2CH(OH)	C ₂₁ H ₂₃ NO ₄
261455	i-Pr	4-Pyr-CH2CH(OH)	C ₁₉ H ₂₁ NO ₃
261456	cyclopentyl	(E)-4-Pyr-CH=CH	C ₂₁ H ₂₁ NO ₂
261457	i-Pr	(E)-4-Pyr-CH=CH	C ₁₉ H ₁₉ NO ₂
261458	cyclopentyl	4-Pyr-CH2CH2	C ₂₁ H ₂₃ NO ₂
261459	cyclopentyl	(Z)-4-Pyr-C(CN)=CH	C ₂₂ H ₂₀ N ₂ O ₂
261460	cyclopentyl	(Z)-3-Pyr-C(CN)=CH	C ₂₂ H ₂₀ N ₂ O ₂
261461	i-Pr	4-Pyr-C(CN)=CH	C ₂₀ H ₁₈ N ₂ O ₂
261462	cyclopentyl	4-Pyr-CH(CN)CH2	C ₂₂ H ₂₂ N ₂ O ₂
261463	cyclopentyl	3-Pyr-CH(CN)CH2	C ₂₂ H ₂₂ N ₂ O ₂
261464	i-Pr	4-Pyr-CH(CN)CH2	C ₂₀ H ₂₀ N ₂ O ₂

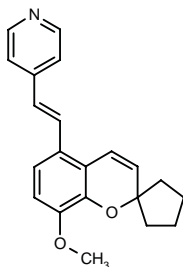
SOURCE – Byk Gulden.

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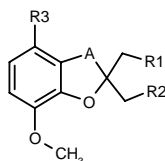
260877

(*E*)-8-Methoxy-5-[2-(4-pyridyl)vinyl]spiro[2*H*-1-benzopyran-2,1'-cyclopentane]



C21-H21-N-O2; Mol wt: 319.40

ACTION – Bronchodilating and antiinflammatory agent, an inhibitor of cyclic AMP phosphodiesterase, particularly type IV (PDE IV; $-\log IC_{50} = 7.10$), reported to possess low toxicity and good bioavailability. Potentially useful for the treatment of asthma, erectile dysfunction and a broad range of chronic and acute inflammatory disorders. Other compounds from this series of 5-substituted-(2*H*)-chromene derivatives include the following:



Compound	R1	R2	R3	A	Formula
261603	-(CH2)2-		4-Pyr-CH2CH(OH)	-CH=CH-	C ₂₁ H ₂₃ NO ₃
261604	-(CH2)2-		4-Pyr-CH2CH2	-(CH2)2-	C ₂₁ H ₂₅ NO ₂
261605	-(CH2)2-		(Z)-4-Pyr-C(CN)=CH	-CH=CH-	C ₂₂ H ₂₀ N ₂ O ₂
261606	H	H	(Z)-4-Pyr-C(CN)=CH	-CH=CH-	C ₂₀ H ₁₈ N ₂ O ₂
261607	H	H	(Z)-3-Pyr-C(CN)=CH	-CH=CH-	C ₂₀ H ₁₈ N ₂ O ₂
261608	H	H	(Z)-2-Pyr-C(CN)=CH	-CH=CH-	C ₂₀ H ₁₈ N ₂ O ₂
261609	-(CH2)2-		4-Pyr-CH(CN)CH2	-(CH2)2-	C ₂₂ H ₂₄ N ₂ O ₂
261610	H	H	4-Pyr-CH(CN)CH2	-(CH2)2-	C ₂₀ H ₂₂ N ₂ O ₂
261611	H	H	2-Pyr-CH(CN)CH2	-(CH2)2-	C ₂₀ H ₂₂ N ₂ O ₂

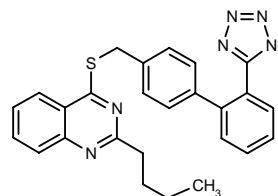
SOURCE – Byk Gulden.

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261132

2-Butyl-4-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl-sulfanyl]quinazoline



C26-H24-N6-S; Mol wt: 452.58

ACTION – Phosphodiesterase type IV (PDE IV) inhibitor with some selectivity relative to type III enzyme (PDE III) ($IC_{50} = 2.9 \pm 0.4$ and 8 ± 1.7 μ M, respectively). Title compound is a lead quinazoline losartan derivative that is undergoing optimization to obtain new agents for the treatment of inflammatory diseases such as asthma.

SOURCE – Almirall Prodesfarma.

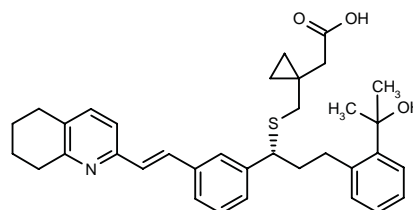
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L-733321

261116

2-[1-[3-[2-(1-Hydroxy-1-methylethyl)phenyl]-1(*R*)-[3-[2(*E*)-(5,6,7,8-tetrahydroquinolin-2-yl)vinyl]phenyl]-propylsulfanylmethyl]cyclopropyl]acetic acid



C35-H41-N-O3-S; Mol wt: 555.77

ACTION – Potent, selective and orally active CysLT₁ (LTD₄) receptor antagonist with the best overall profile from a series of pyridyl analogs of montelukast. It inhibited [³H]-LTD₄ binding in guinea pig lung membranes ($IC_{50} = 0.19 \pm 0.05$ nM vs. 0.64 ± 0.36 nM for montelukast; $IC_{50} = 1.8 \pm 0.6$ nM vs. 0.43 ± 0.17 nM for montelukast in the presence of human serum albumin) and in U937 cells ($IC_{50} = 0.25 \pm 0.11$ nM vs. 0.78 ± 0.35 nM for montelukast). The compound possesses an excellent pharmacokinetic profile in animals, with a bioavailability of 39 and 40%, respectively, in rats and squirrel monkeys, and high C_{max} values and a long half-life (at least 6 h) in the latter species after an oral dose of 10 mg/kg. In conscious squirrel monkeys, it produced 72% inhibition of the increase in pulmonary airflow resistance and 90% inhibition of the decrease in dynamic compliance induced by aerosol LTD₄ challenge when given 4 h prior to challenge at a dose of 0.01 mg/kg p.o.

SOURCE – Merck Frosst.

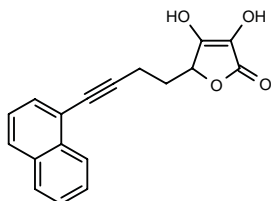
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260682

3,4-Dihydroxy-5-[4-(1-naphthyl)-3-butynyl]-2(5*H*)-furanone



C18-H14-O4; Mol wt: 294.31

ACTION – Antioxidant with dual cyclooxygenase (COX)- and 5-lipoxygenase-inhibitory activity. The compound inhibited COX-1 by 34% and COX-2 by 22% at 300 μ M, and 5-lipoxygenase with an IC_{50} of 0.3 μ M. It also inhibited CCl_4 -induced lipid peroxidation of polyunsaturated fatty acids from guinea pig liver microsomes (73% inhibition at 300 μ M). The compound potently inhibited lipopolysaccharide (LPS)-induced NF- κ B nuclear translocation (90% at 30 nM).

Such compounds may provide superior antiinflammatory activity and reduced side effects compared to conventional therapies for the treatment of disorders including asthma, rheumatoid arthritis, irritable bowel syndrome, ischemia/reperfusion injury, atherosclerosis, restenosis and neurodegenerative disorders.

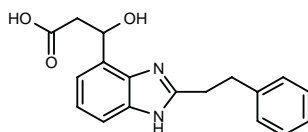
SOURCE – Oxis.

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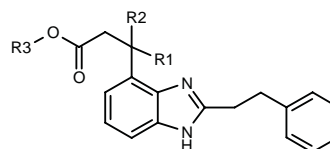
261202

3-Hydroxy-3-[2-(2-phenylethyl)-1*H*-benzimidazol-4-yl]propionic acid



C18-H18-N2-O3; Mol wt: 310.35

ACTION – Agent for the treatment of asthma and allergic disorders proven to inhibit antigen-induced eosinophil infiltration into the peritoneal cavity of mice (55% inhibition at 0.3 mg/kg/day p.o. x 10 days vs. 61-85% for prednisolone acetate at 10 mg/kg/day p.o. x 10 days). No deaths were observed following oral administration of 100 mg/kg/day x 7 days to mice. A representative compound from a series of benzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
261922		-O-	H	C ₁₈ H ₁₆ N ₂ O ₃
261923		-O-	Me	C ₁₉ H ₁₈ N ₂ O ₃
261924		-O-	Et	C ₂₀ H ₂₀ N ₂ O ₃
261925	H	OH	Me	C ₁₉ H ₂₀ N ₂ O ₃
261926	H	OH	Et	C ₂₀ H ₂₂ N ₂ O ₃

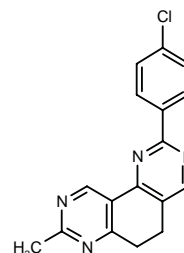
SOURCE – Mochida.

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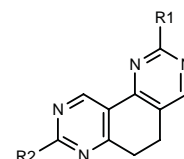
261210

2-(4-Chlorophenyl)-8-methyl-5,6-dihydropyrimido-[4,5-*f*]quinazoline



C17-H13-Cl-N4; Mol wt: 308.77

ACTION – Antiallergic and antiinflammatory agent with potential in the treatment of asthma, rhinitis, atopic dermatitis, bronchitis and chronic graft-versus-host disease. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	R2	Formula
261597	4-Cl-Ph	NH2	C ₁₆ H ₁₂ ClN ₅
261598	3-Pyr	H	C ₁₅ H ₁₁ N ₅
261599	2-Pyr	H	C ₁₅ H ₁₁ N ₅
261600	1-oxido-3-Pyr	H	C ₁₅ H ₁₁ N ₅ O
261601	6-Me-3-Pyr	H	C ₁₆ H ₁₃ N ₅
261602	6-Me-1-oxido-3-Pyr	NH2	C ₁₆ H ₁₄ N ₅ O

SOURCE – Astra.

REFERENCES

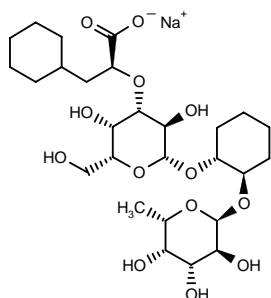
1. Bantick, J. et al. (Astra Pharm., Ltd.; Astra AB) *Novel cpds*. WO 9801449.

CGP-69669A

247695

(1*R*-*trans*)-1-[3-*O*-[1(*S*)-Carboxy-2-cyclohexylethyl]-β-D-galactopyranosyloxy]-2-(6-deoxy-α-L-galactopyranosyloxy)cyclohexane sodium salt

(1*R*,2*R*)-3-*O*-[1(*S*)-Carboxy-2-cyclohexylethyl]-2-(6-deoxy-α-L-galactopyranosyloxy)cyclohexyl-β-D-galactopyranoside monosodium salt



C27-H45-Na-O13; Mol wt: 600.63

ACTION – Potential antiinflammatory agent, a sialyl Lewis^x (sLe^x) mimetic that acts as a selective E-selectin antagonist. It was able to reduce the number and increase the velocity of rolling leukocytes *in vivo* in mice stimulated with TNF-α (tumor necrosis factor-α).

SOURCE – Novartis.

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1. Kolb, H.C. (Ciba-Geigy AG) *Diglycosylated 1,2-diols as mimetics of sialyl-Lewis X and sialyl-Lewis A*. WO 9701569.
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EPI-2010

261658

Phosphorothioate antisense oligodeoxynucleotide whose sequence is: 5'-GATGGAGGGCGGCATGGCGGG-3'

Slightly yellowish crystalline solid.

ACTION – Highly soluble and stable phosphorothioate antisense oligonucleotide targeting the human adenosine A₁ receptor that acts by downregulating the receptor. It has proven effective in animal models of asthma, relieving both the acute bronchoconstrictor and chronic inflammatory components of the disease. Aerosolized oligonucleotide exhibited gene-specific effects in rabbits and desensitized animals to subsequent challenge with adenosine or allergen, without apparent toxicity.

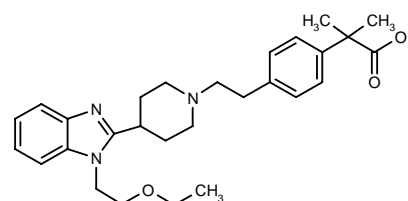
SOURCES – East Carolina Univ., Greenville, NC (US); EpiGenesis.

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1. McKenna, M. et al. *Duration of effect of a respirable antisense oligonucleotide (Rason) EPI 2010 for the adenosine A₁ receptor*. J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 967.
2. Nyce, J.W. *Respirable antisense oligonucleotides as novel therapeutic agents for asthma and other pulmonary diseases*. Exp Opin Invest Drugs 1997, 6(9): 1.
3. Nyce, J.W. and Metzger, W.J. *DNA antisense therapy for asthma in an animal model*. Nature 1997, 385(6618): 721.
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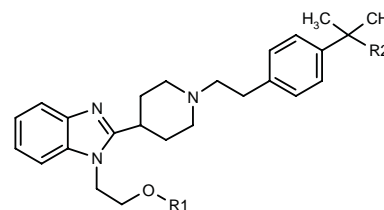
260868

2-[4-[2-[4-[1-(2-Ethoxyethyl)benzimidazol-2-yl]piperidin-1-yl]ethyl]phenyl]-2-methylproionic acid



C28-H37-N3-O3; Mol wt: 463.62

ACTION – Antiallergic agent with potent antihistaminic activity, as demonstrated *in vitro* by inhibition of histamine-induced guinea pig ileum contractions. *In vivo* it inhibited the histamine-induced increase in vascular permeability with a long duration of action, producing > 50% inhibition for over 6 h at 5 mg/kg p.o. Compound was devoid of CNS side effects in rats at 100 mg/kg p.o. and no effects on ECG or Q-T_c interval were observed following i.v. administration of 20 mg/kg. Other specifically claimed compounds from this series of benzimidazole derivatives include the following:



Compound	R1	R2	Formula
261264	Et	4,4-(Me)2-4,5-dihydro-2-oxazolyl	C ₃₂ H ₄₄ N ₄ O ₂
261265	Et	CO ₂ Et	C ₃₀ H ₄₁ N ₃ O ₃
261266	Et	CH ₂ OH	C ₂₈ H ₃₉ N ₃ O ₂
261267	H	4,4-(Me)2-4,5-dihydro-2-oxazolyl	C ₃₀ H ₄₀ N ₄ O ₂
261268	H	CO ₂ H	C ₂₆ H ₃₃ N ₃ O ₃

SOURCE – FAES.

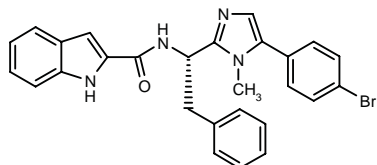
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TREATMENT OF RDS AND EMPHYSEMA

259863

N-[1(*S*)-[5-(4-Bromophenyl)-1-methylimidazol-2-yl]-2-phenylethyl]-1*H*-indole-2-carboxamide



C27-H23-Br-N4-O; Mol wt: 499.41

ACTION – Agent for the treatment of adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, septic shock, heart failure and the like, an inhibitor of the production of nitric oxide (NO), as demonstrated in the murine macrophage cell line RAW 264.7 (100% inhibition at 10 μ M). A representative compound within a series of indolyl and benzofuranyl carboxamides.

SOURCE – Fujisawa.

REFERENCES

1. Itoh, Y. et al. (Fujisawa Pharm. Co., Ltd.) *New indolyl and benzofuranyl carboxamides as inhibitors of nitric oxide production*. WO 9745425.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

FENOLDOPAM MESILATE

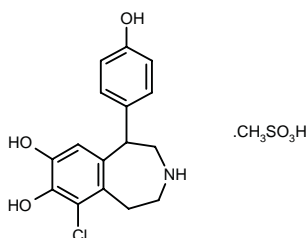
Rec INN; BAN; USAN

090634

6-Chloro-7,8-dihydroxy-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine methanesulfonate

6-Chloro-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol methanesulfonate

SK&F-82526J⁺



C16-H16-Cl-N-O3.C-H4-O3-S; Mol wt: 401.86

ACTION – Rapid-acting vasodilator, a potent dopamine D₁ receptor agonist with moderate affinity for α_2 -adrenoceptors and no significant affinity for other receptors.

INDICATION – In-hospital, short-term (up to 48 h) management of severe hypertension when a rapid but quickly reversible emergency reduction in blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function.

PRESENTATION – Single-dose ampules (5 ml), each ml of solution containing fenoldopam mesilate equiv. to 10 mg fenoldopam.

PROPRIETARY NAME – *Corlopad* (US).

SOURCE – Neurex; licensed from SmithKline Beecham.

RECENT REFERENCES

1. Calhoun, D. et al. *Fenoldopam: A novel, peripherally acting dopamine-1 agonist for parenteral treatment of hypertension*. Med Actual/Drugs Today 1997, 33(10): 729.
2. Dunbar, L. et al. *Emergency department management of hypertensive emergencies: A comparison of Corlopad® versus sodium nitroprusside*. Amer J Hypertension 1997, 10(4, Part 2): 91A.
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9. Taylor, A. et al. *Therapeutic implications of fenoldopam pharmacokinetic/pharmacodynamic modeling in hypertensive patients*. Amer J Hypertension 1997, 10(4, Part 2): 106A.
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11. *FDA advisory committee recommends Corlopad approval*. Prous Science Daily Essentials June 30, 1997.
12. *FDA grants final marketing approval for Corlopad*. Prous Science Daily Essentials September 25, 1997.
13. *Fenoldopam mesylate launch*. Neurex Corp. Company Communication 1998, February 5.
14. *Neurex announces Corlopad partner in Europe; Beaufour Ipsen to launch product into hospital market*. Neurex Corp. Press Release 1996, October 1.
15. *Neurex announces FDA panel recommends approval of Corlopad for blood pressure control in the hospital setting*. Neurex Corp. Press Release 1997, June 26.
16. *Neurex' Corlopad demonstrates sustained effect on blood pressure and renal function*. Neurex Corp. Press Release 1996, May 20.
17. *Neurex files NDA for Corlopad*. Neurex Corp. Press Release 1996, June 25.
18. *Neurex initiates Corlopad renal program; studies focused on beneficial effect on the kidney*. Neurex Corp. Press Release 1997, February 5.
19. *Neurex receives final approval for Corlopad*. Neurex Corp. Press Release 1997, September 24.

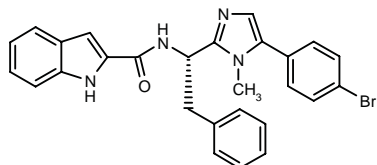
MONOGRAPH – SKF-82526J. Drugs Fut 1982, 7(1): 32.

⁺ Annu Drug Data Rep 1982, 4: 185.

TREATMENT OF RDS AND EMPHYSEMA

259863

N-[1(*S*)-[5-(4-Bromophenyl)-1-methylimidazol-2-yl]-2-phenylethyl]-1*H*-indole-2-carboxamide



C27-H23-Br-N4-O; Mol wt: 499.41

ACTION – Agent for the treatment of adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, septic shock, heart failure and the like, an inhibitor of the production of nitric oxide (NO), as demonstrated in the murine macrophage cell line RAW 264.7 (100% inhibition at 10 μ M). A representative compound within a series of indolyl and benzofuranyl carboxamides.

SOURCE – Fujisawa.

REFERENCES

1. Itoh, Y. et al. (Fujisawa Pharm. Co., Ltd.) *New indolyl and benzofuranyl carboxamides as inhibitors of nitric oxide production*. WO 9745425.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

FENOLDOPAM MESILATE

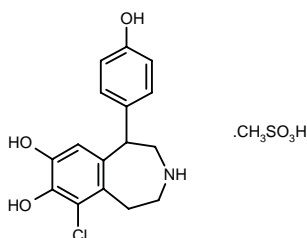
Rec INN; BAN; USAN

090634

6-Chloro-7,8-dihydroxy-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine methanesulfonate

6-Chloro-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol methanesulfonate

SK&F-82526J⁺



C16-H16-Cl-N-O3.C-H4-O3-S; Mol wt: 401.86

ACTION – Rapid-acting vasodilator, a potent dopamine D₁ receptor agonist with moderate affinity for α_2 -adrenoceptors and no significant affinity for other receptors.

INDICATION – In-hospital, short-term (up to 48 h) management of severe hypertension when a rapid but quickly reversible emergency reduction in blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function.

PRESENTATION – Single-dose ampules (5 ml), each ml of solution containing fenoldopam mesilate equiv. to 10 mg fenoldopam.

PROPRIETARY NAME – *Corlopad* (US).

SOURCE – Neurex; licensed from SmithKline Beecham.

RECENT REFERENCES

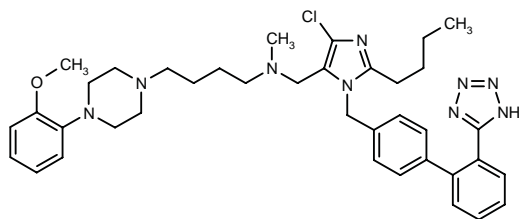
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3. El-Tahtawy, A. et al. *Dual effect PK/PD modeling of intravenous fenoldopam in moderate hypertensive patients*. Clin Pharmacol Ther 1998, 63(2): Abst PI-102.
4. Everitt, D.E. et al. *Effect of intravenous fenoldopam on intraocular pressure in ocular hypertension*. J Clin Pharmacol 1997, 37(4): 312.
5. Grevel, J. et al. *PK/PD analysis of intravenous fenoldopam in hypertensive emergencies*. Clin Pharmacol Ther 1998, 63(2): Abst PI-82.
6. Grevel, J. et al. *PK/PD analysis of intravenous fenoldopam in hypertensive patients*. Clin Pharmacol Ther 1998, 63(2): Abst PI-83.
7. Klecker, R.W. and Collins, J.M. *Stereoselective metabolism of fenoldopam and its metabolites in human liver microsomes, cytosol, and slices*. J Cardiovasc Pharmacol 1997, 30(1): 69.
8. Post, J.B. IV and Frishman, W.H. *Fenoldopam: A new dopamine agonist for the treatment of hypertensive urgencies and emergencies*. J Clin Pharmacol 1998, 38(1): 2.
9. Taylor, A. et al. *Therapeutic implications of fenoldopam pharmacokinetic/pharmacodynamic modeling in hypertensive patients*. Amer J Hypertension 1997, 10(4, Part 2): 106A.
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14. *Neurex announces Corlopad partner in Europe; Beaufour Ipsen to launch product into hospital market*. Neurex Corp. Press Release 1996, October 1.
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16. *Neurex' Corlopad demonstrates sustained effect on blood pressure and renal function*. Neurex Corp. Press Release 1996, May 20.
17. *Neurex files NDA for Corlopad*. Neurex Corp. Press Release 1996, June 25.
18. *Neurex initiates Corlopad renal program; studies focused on beneficial effect on the kidney*. Neurex Corp. Press Release 1997, February 5.
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MONOGRAPH – SKF-82526J. Drugs Fut 1982, 7(1): 32.

⁺ Annu Drug Data Rep 1982, 4: 185.

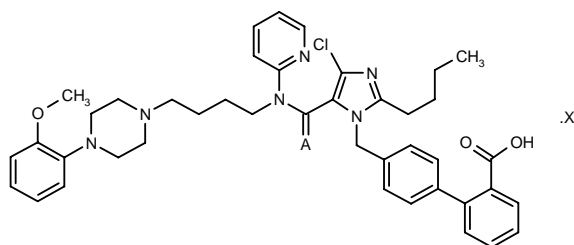
258442

N-[2-Butyl-4-chloro-1-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-ylmethyl]-*N*-[4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl]-*N*-methylamine



C₃₈H₄₈ClN₉O; Mol wt: 682.31

ACTION – Antihypertensive agent, an angiotensin II antagonist ($pA_2 = 8.5$) with additional activity as an α_1 -adrenoceptor antagonist ($pA_2 = 6.8$), shown to cause a decrease of 34 mmHg in blood pressure in spontaneously hypertensive rats at 30 mg/kg intragastrically. Other compounds from this series of imidazole derivatives include the following:



Compound	A	X	Formula
260838	H ₂	1/2H ₂ O	C ₄₂ H ₄₉ ClN ₆ O ₃ ·1/2H ₂ O
260839	O		C ₄₂ H ₄₇ ClN ₆ O ₄

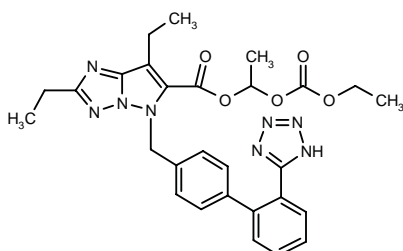
SOURCE – Kyorin.

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260825

(±)-2,7-Diethyl-5-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5*H*-pyrazolo[1,5-*b*][1,2,4]triazole-6-carboxylic acid 1-(ethoxycarbonyloxy)ethyl ester



C₂₈H₃₀N₈O₅; Mol wt: 558.60

M.p. 80-3 °C.

ACTION – Antihypertensive agent, a double ester prodrug of a potent angiotensin II (All) antagonist ($pD_2' = 9.31$ for inhibition of All-induced contractions in rabbit thoracic aorta strips) designed to improve the oral activity of the parent acid. In an *in vivo* model of All-induced pressor response in conscious rats, orally administered prodrug showed long-lasting (> 24 h) hypotensive activity, with 42 and 91% inhibition, respectively, at 8 h after 3 and 30 mg/kg vs. 34 and 52% inhibition, respectively, at 30 mg/kg for the parent acid and losartan. The prodrug was also tested in furosemide-treated dogs and gave a maximal decrease in mean blood pressure of 37 mmHg at 10 mg/kg p.o., being 10-fold more potent than losartan.

SOURCE – Yamanouchi.

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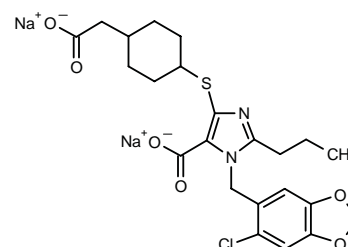
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RU-69986*

260341

252074 (as free acid)

4-[4-(Carboxymethyl)cyclohexylsulfanyl]-1-(6-chloro-1,3-benzodioxol-5-ylmethyl)-2-propyl-1*H*-imidazole-5-carboxylic acid disodium salt



C₂₃H₂₅ClN₂Na₂O₆S; Mol wt: 538.95

ACTION – Nonpeptide endothelin receptor antagonist showing some specificity for ET_A receptors over ET_B receptors ($IC_{50} = 2$ and 52 nM, respectively, for displacement of [¹²⁵I]-ET-1 binding in human neuroblastoma SK-N-SH [ET_A] cells and human megakaryoblastic MEG-01 cells [ET_B]). It competitively antagonized ET-1-induced contractions in rat endothelium-denuded aorta (ET_A), being more potent than bosentan. Compound also antagonized the contractile responses to ET-1 and sarafatoxin S6C in rat portal vein and inhibited the sarafatoxin S6C-induced relaxation of rat mesenteric artery precontracted by norepinephrine (ET_B).

SOURCE – Hoechst Marion Roussel.

REFERENCES

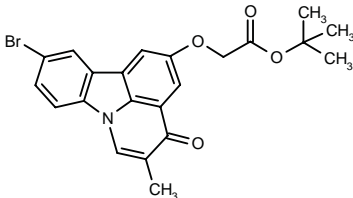
1. Heckmann, B. et al. (Roussel-Uclaf) *Novel imidazole N-benzylidioxol derivs., method for preparing same, resulting intermediates, pharmaceutical compsns. and use of said derivs. as endothelin antagonists.* FR 2740774, WO 9717339.

2. Chevillard, C. et al. *In vitro characterization of RU 69986, a novel non-peptide endothelin receptor antagonist. Comparison with bosentan.* IBC Conf Endothel Inhib. Adv Ther Appl Dev (June 26-27, Philadelphia) 1997.

*Identified compound **252074** Drug Data Rep 1997, 19(8): 707.

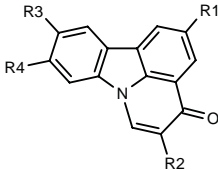
259865

2-(10-Bromo-5-methyl-4-oxo-4*H*-pyrido[3,2,1-*jk*]carbazol-2-yloxy)]acetic acid *tert*-butyl ester



C22-H20-Br-N-O4; Mol wt: 442.31

ACTION – Agent for the treatment of pulmonary hypertension and ischemic heart disease, a potent and selective cGMP phosphodiesterase type V (PDE V) inhibitor (IC₅₀ = 0.0015 μM; IC₅₀ > 30 μM against type III and type I enzymes). Compound was particularly potent in lowering pulmonary artery blood pressure as compared to systemic blood pressure in dogs (33% vs. 13% decrease at 0.3 mg/kg i.v.; nifedipine: 3% vs. 18% decrease at 0.01 mg/kg i.v.). No toxic effects were observed at 100 mg/kg/day x 4 days p.o. in rats. Within a wide series of pyridocarbazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
261332	t-BuOCOCH2O	3-Pyr-CH2	Br	H	C ₂₇ H ₂₃ BrN ₂ O ₄
261333	t-BuOCOCH2O	H	Br	H	C ₂₁ H ₁₈ BrNO ₄
261334	OH	3-Pyr-CH2	H	Br	C ₂₁ H ₁₃ BrN ₂ O ₂
261335	3-Pyr-CH2O	3-Pyr-CH2	H	Br	C ₂₇ H ₁₈ BrN ₃ O ₂
261336	OCH2CONHEt	3-Pyr-CH2	H	Br	C ₂₆ H ₂₀ BrN ₃ O ₃
261337	O(CH2)3OH	3-Pyr-CH2	H	Br	C ₂₄ H ₁₉ BrN ₂ O ₃
261338	H	H	Cl	H	C ₁₅ H ₈ ClNO

SOURCE – Mochida.

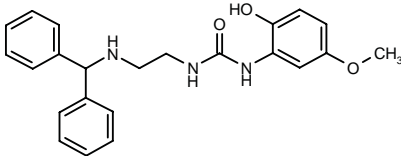
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

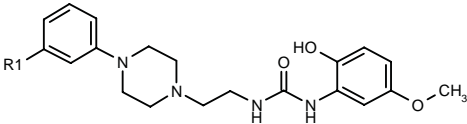
257485

1-[2-(Diphenylmethylamino)ethyl]-3-(2-hydroxy-5-methoxyphenyl)urea

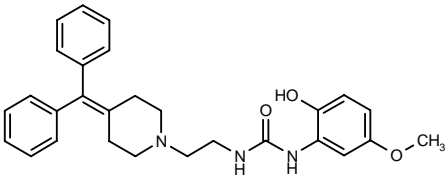


C23-H25-N3-O3; Mol wt: 391.47

ACTION – Agent for the treatment or prevention of atherosclerosis, inflammatory and ischemic disorders reported to exhibit lipid peroxidation-, macrophage foaming- and ACAT-inhibitory effects, as well as an inhibitory effect against reperfusion-induced arrhythmia. Within this series of phenol derivatives, the following are also included:



Compound	R1	Formula
260736	CF3	C ₂₁ H ₂₅ F ₃ N ₄ O ₃
260737	H	C ₂₀ H ₂₆ N ₄ O ₃



260735: C28-H31-N3-O3

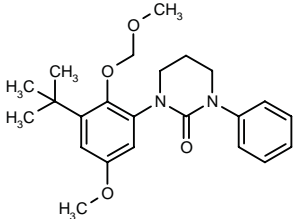
SOURCE – Tanabe Seiyaku.

REFERENCES

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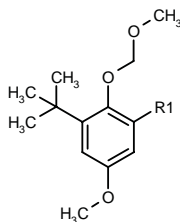
257486

1-[3-*tert*-Butyl-2-(methoxymethoxy)-5-methoxyphenyl]-3-phenylhexahydropyrimidin-2-one

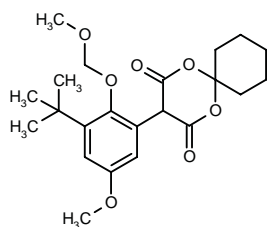


C23-H30-N2-O4; Mol wt: 398.50

ACTION – Antiatherosclerotic, antiischemic and anti-inflammatory agent reported to possess lipid peroxidation-, macrophage foaming- and ACAT-inhibitory effects. Other related compounds include the following:



Compound	R1	Formula
261693	3-Pyr-CH ₂ NHCO	C ₂₀ H ₂₆ N ₂ O ₄
261694	NHSO ₂ Me	C ₁₄ H ₂₃ NO ₅ S
261695	NHSO ₂ Ph	C ₁₉ H ₂₅ NO ₅ S
261696	4-Me-PhSO ₂ NH	C ₂₀ H ₂₇ NO ₅ S
261697	2-benzoxazolyl-NH	C ₂₀ H ₂₄ N ₂ O ₄
261699	CH(1-imidazolyl)(CH ₂) ₅ CO ₂ H	C ₂₃ H ₃₄ N ₂ O ₅



261698: C₂₂-H₃₀-O₇

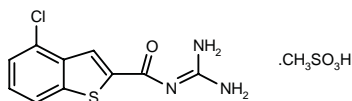
SOURCE – Tanabe Seiyaku.

REFERENCES

1. Suzuki, T. et al. (Tanabe Seiyaku Co., Ltd.) *Phenol derivs.* JP 97278741.

257488

N-(4-Chlorobenzo[*b*]thiophen-2-ylcarbonyl)guanidine methanesulfonate



C₁₀-H₈-Cl-N₃-O-S-C-H₄-O₃-S; Mol wt: 349.81

ACTION – An Na⁺/H⁺ exchange inhibitor with a K_i value of < 0.1 μM in rat thymus gland cell preparations. A representative compound within a series of guanidine derivatives.

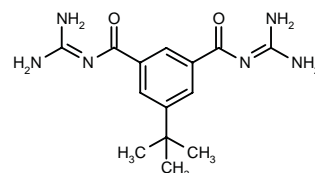
SOURCE – Fujisawa.

REFERENCES

1. Hisano, A. et al. (Fujisawa Pharm. Co., Ltd.) *Novel guanidine derivs.* JP 97278767.

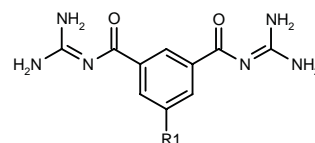
261495

4-*tert*-Butyl-*N,N'*-(diaminomethylene)isophthalamide



C₁₄-H₂₀-N₆-O₂; Mol wt: 304.35

ACTION – Antiarrhythmic agent with a cardioprotective component that exerts its action by virtue of its Na⁺/H⁺ exchange-inhibitory activity. Potentially useful for the treatment or prevention of myocardial infarction, angina pectoris and cardiac and cerebral ischemic disorders. Other specifically claimed compounds from this series of benzenedicarboxylic acid diguanides include the following:



Compound	R1	Formula
261679	3,5-(CF ₃) ₂ -Ph	C ₁₈ H ₁₄ F ₆ N ₆ O ₂
261680	3,5-(Cl) ₂ -Ph	C ₁₆ H ₁₄ Cl ₂ N ₆ O ₂
261681	2,4-(Cl) ₂ -Ph	C ₁₆ H ₁₄ Cl ₂ N ₆ O ₂
261682	3-Cl-4-F-Ph	C ₁₆ H ₁₄ ClFN ₆ O ₂
261683	cyclohexyl	C ₁₆ H ₂₂ N ₆ O ₂

SOURCE – Hoechst Marion Roussel.

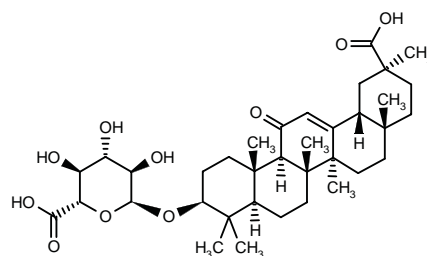
REFERENCES

1. Kleemann, H.-W. et al. (Hoechst AG) *Substd. benzenedicarboxylic acid diguanides, process for their preparation, their use as a medicament or diagnostic, and medicament containing them.* US 5731350.

GM-3290

261294

(2*S*,4*aS*,6*aS*,6*bR*,8*aS*,10*S*,12*aS*,12*bR*,14*bR*)-10-(α-D-Glucopyranosyloxyuronic acid)-2,4*a*,6*a*,6*b*,9,9,12*a*-heptamethyl-13-oxo-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,12*b*,13,14*b*-icosahydricene-2-carboxylic acid



C₃₆-H₅₄-O₁₀; Mol wt: 646.82

ACTION – Glycomimetic glycyrrhizin analog with cardioprotective effects and the ability to inhibit P-selectin-mediated neutrophil adhesion, and possibly also L-selectin-mediated adhesion. The compound (0.1 μ M) significantly inhibited neutrophil adhesion in human umbilical vein endothelial cell (HUVEC) monolayers incubated with C5a. In rabbits subjected to occlusion of the left coronary artery followed by reperfusion, GM-3290 (10 mg/kg/h i.v. immediately before reperfusion and every hour during reperfusion) significantly reduced myocardial infarct size and myocardial myeloperoxidase content in the area at risk.

SOURCE – Glycomed.

REFERENCES

1. Kilgore, K.S. et al. *Reduction of myocardial infarct size in vivo by carbohydrate-based glycomimetics*. J Pharmacol Exp Ther 1998, 284(1): 427.

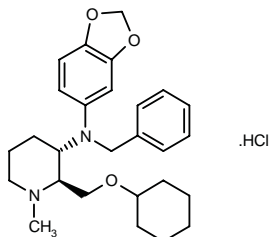
ORG-13061

256849

(\pm)-*trans*-N-(1,3-Benzodioxol-5-yl)-N-benzyl-2-(cyclohexyloxymethyl)-1-methylpiperidine-3-amine monohydrochloride

Org-13471 [as (–)-enantiomer]

Org-13581 [as (+)-enantiomer]



C27-H36-N2-O3.HCl; Mol wt: 473.05

ACTION – Potential antiatherosclerotic agent with calcium-antagonist and antioxidant properties. It inhibited K^+ -induced contractions in rabbit aortic rings (IC_{50} = 0.50 μ M) without affecting phenylephrine-induced contractions, and it induced a concentration-dependent inhibition of slow calcium current-mediated action potentials in guinea pig papillary muscle (IC_{50} = 0.82 μ M). The compound displayed selectivity for vascular relative to cardiac contractions. Copper ion-induced human LDL peroxidation was inhibited at concentrations of 0.1-1 μ M, as was lipid accumulation by rat aortic smooth muscle cells in culture at concentrations of 1-3 μ M. The calcium channel-blocking activity appears to reside mainly in the (–)-enantiomer, whereas the (+)- and (–)-enantiomers were equipotent as regards antioxidant activity.

SOURCES – Organon; Riom Labs.-CERM.

REFERENCES

1. Carlier, P. et al. (Riom Labs.-CERM SA) *Novel Subst. 3-piperidine amines or 3-azepine amines, their preparation and their applications in therapeutic*. AU 8782856, EP 275759, FR 2608602, JP 88190876, US 4822792.

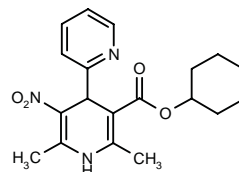
2. Beaughard, M. et al. *In vitro calcium antagonistic and antioxidant effects of Org 13061 and its enantiomers, new potential antiatherosclerotic compounds*. Fundam Clin Pharmacol 1997, 11(5): 416.

HEART FAILURE THERAPY

260684

(+)-2,6-Dimethyl-5-nitro-4-(2-pyridyl)-1,4-dihydropyridine-3-carboxylic acid cyclohexyl ester

(+)-2',6'-Dimethyl-5'-nitro-1',4'-dihydro[2,4'-bipyridine]-3'-carboxylic acid cyclohexyl ester



C19-H23-N3-O4; Mol wt: 357.41

Yellow solid, m.p. 188 °C, $[\alpha]_D^{23} +146.7^\circ$ (c 0.37, CHCl₃).

ACTION – A dual cardioselective calcium channel agonist and smooth muscle-selective calcium channel antagonist with potential in the treatment of congestive heart failure. The compound demonstrated calcium channel-antagonist effects in guinea pig ileum longitudinal smooth muscle (IC_{50} = 5.27 \pm 0.26 μ M) and calcium channel-agonist effects in guinea pig left atrium (EC_{50} = 8.45 \pm 1.55 μ M).

SOURCE – Univ. Alberta, Alberta (CA).

REFERENCES

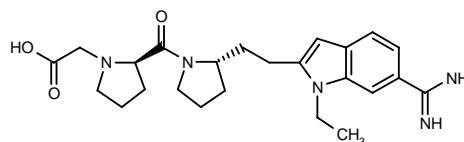
1. Ramesh, M. et al. *Synthesis and calcium channel-modulating effects of alkyl (or cycloalkyl) 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridyl-5-pyridinecarboxylate racemates and enantiomers*. J Med Chem 1998, 41(4): 509.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

259862

2-[2(R)-[2(S)-[2-(6-Amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-1-yl]carbonyl]pyrrolidin-1-yl]acetic acid



C24-H33-N5-O3; Mol wt: 439.56

ACTION – Glycomimetic glycyrrhizin analog with cardioprotective effects and the ability to inhibit P-selectin-mediated neutrophil adhesion, and possibly also L-selectin-mediated adhesion. The compound (0.1 μ M) significantly inhibited neutrophil adhesion in human umbilical vein endothelial cell (HUVEC) monolayers incubated with C5a. In rabbits subjected to occlusion of the left coronary artery followed by reperfusion, GM-3290 (10 mg/kg/h i.v. immediately before reperfusion and every hour during reperfusion) significantly reduced myocardial infarct size and myocardial myeloperoxidase content in the area at risk.

SOURCE – Glycomed.

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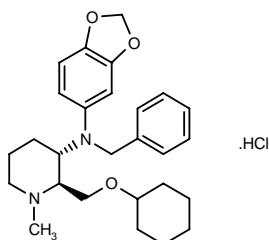
ORG-13061

256849

(\pm)-*trans*-N-(1,3-Benzodioxol-5-yl)-N-benzyl-2-(cyclohexyloxymethyl)-1-methylpiperidine-3-amine monohydrochloride

Org-13471 [as (–)-enantiomer]

Org-13581 [as (+)-enantiomer]



C27-H36-N2-O3.HCl; Mol wt: 473.05

ACTION – Potential antiatherosclerotic agent with calcium-antagonist and antioxidant properties. It inhibited K^+ -induced contractions in rabbit aortic rings (IC_{50} = 0.50 μ M) without affecting phenylephrine-induced contractions, and it induced a concentration-dependent inhibition of slow calcium current-mediated action potentials in guinea pig papillary muscle (IC_{50} = 0.82 μ M). The compound displayed selectivity for vascular relative to cardiac contractions. Copper ion-induced human LDL peroxidation was inhibited at concentrations of 0.1-1 μ M, as was lipid accumulation by rat aortic smooth muscle cells in culture at concentrations of 1-3 μ M. The calcium channel-blocking activity appears to reside mainly in the (–)-enantiomer, whereas the (+)- and (–)-enantiomers were equipotent as regards antioxidant activity.

SOURCES – Organon; Riom Labs.-CERM.

REFERENCES

1. Carlier, P. et al. (Riom Labs.-CERM SA) *Novel Subst. 3-piperidine amines or 3-azepine amines, their preparation and their applications in therapeutic*. AU 8782856, EP 275759, FR 2608602, JP 88190876, US 4822792.

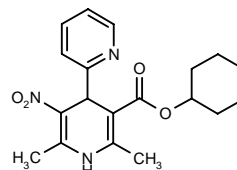
2. Beaughard, M. et al. *In vitro calcium antagonistic and antioxidant effects of Org 13061 and its enantiomers, new potential antiatherosclerotic compounds*. Fundam Clin Pharmacol 1997, 11(5): 416.

HEART FAILURE THERAPY

260684

(+)-2,6-Dimethyl-5-nitro-4-(2-pyridyl)-1,4-dihydropyridine-3-carboxylic acid cyclohexyl ester

(+)-2',6'-Dimethyl-5'-nitro-1',4'-dihydro[2,4'-bipyridine]-3'-carboxylic acid cyclohexyl ester



C19-H23-N3-O4; Mol wt: 357.41

Yellow solid, m.p. 188 °C, $[\alpha]_D^{23} +146.7^\circ$ (c 0.37, CHCl₃).

ACTION – A dual cardioselective calcium channel agonist and smooth muscle-selective calcium channel antagonist with potential in the treatment of congestive heart failure. The compound demonstrated calcium channel-antagonist effects in guinea pig ileum longitudinal smooth muscle (IC_{50} = 5.27 \pm 0.26 μ M) and calcium channel-agonist effects in guinea pig left atrium (EC_{50} = 8.45 \pm 1.55 μ M).

SOURCE – Univ. Alberta, Alberta (CA).

REFERENCES

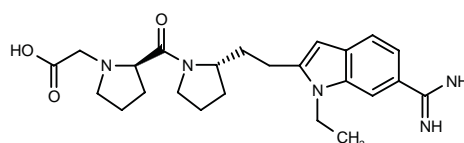
1. Ramesh, M. et al. *Synthesis and calcium channel-modulating effects of alkyl (or cycloalkyl) 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridyl-5-pyridinecarboxylate racemates and enantiomers*. J Med Chem 1998, 41(4): 509.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

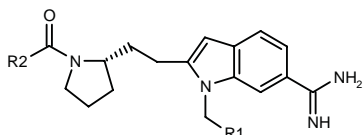
259862

2-[2(*R*)-[2(*S*)-[2-(6-Amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-1-yl]carbonyl]pyrrolidin-1-yl]acetic acid



C24-H33-N5-O3; Mol wt: 439.56

ACTION – Anticoagulant and antithrombotic agent, a potent, selective and orally active inhibitor of human thrombin (IC_{50} = 15.9 nM; IC_{50} trypsin = 128.0 nM). Thrombin time (TT) was determined in rat plasma before and after administration of test compound; the TT ratio (after/before) was 2.62 at a dose of 30 mg/kg p.o. and 7.83 at a dose of 50 mg/kg p.o. It also displayed a good pharmacokinetic profile in rats, with a half-life of 64 min and a bioavailability of 32.6%. A representative compound within a series of aromatic amidine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
260651	Me	2-CO ₂ H-PhCH ₂	C ₂₆ H ₃₀ N ₄ O ₃
260652	H	1-(EtOCOCH ₂)-2(R)-pyrrolidinyl	C ₂₅ H ₃₅ N ₅ O ₃
260653	Me	1-(H-Ala-)-2(R)-pyrrolidinyl	C ₂₅ H ₃₆ N ₆ O ₂

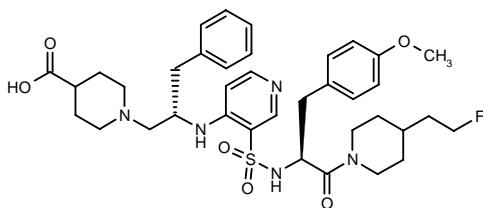
SOURCE – C & C Research Labs.

REFERENCES

1. Koo, B.A. et al. (C&C Res. Labs.) *Aromatic amidine derivs. useful as selective thrombin inhibitors*. WO 9745424.

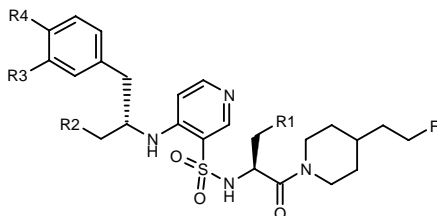
260070

1-[2(S)-[3-[N-[2-[4-(2-Fluoroethyl)piperidin-1-yl]-1(S)-(4-methoxybenzyl)-2-oxoethyl]sulfamoyl]pyridin-4-ylamino]-3-phenylpropyl]piperidine-4-carboxylic acid



C37-H48-F-N5-O6-S; Mol wt: 709.87

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of thrombin (K_i = 6 nM against human α -thrombin). Compound was found to double the activated partial thromboplastin time (APTT) in human plasma at 1.5 μ M. Other exemplified compounds from this series of pyridylsulfonamides include the following:



Compound	R1	R2	R3	R4	Formula
261252	2-benzothiazolyl	OH	H	H	C ₃₁ H ₃₆ FN ₅ O ₄ S ₂
261253	2-benzothiazolyl	OH	H	OMe	C ₃₂ H ₃₈ FN ₅ O ₅ S ₂
261254	2-benzothiazolyl	OCH ₂ CH ₂ OH	H	H	C ₃₃ H ₄₀ FN ₅ O ₅ S ₂
261255	4-OH-Ph	OH	OMe	OMe	C ₃₂ H ₄₁ FN ₄ O ₇ S
261256	4-MeO-Ph	4-OH-1-Pip	H	H	C ₃₆ H ₄₈ FN ₅ O ₅ S

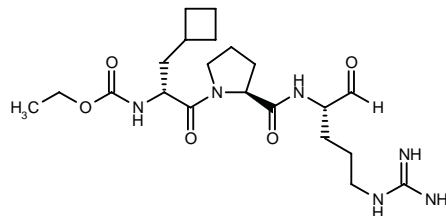
SOURCE – Novartis.

REFERENCES

1. Brundish, D.E. et al. (Novartis AG) *Thrombin inhibitors*. WO 9746553.

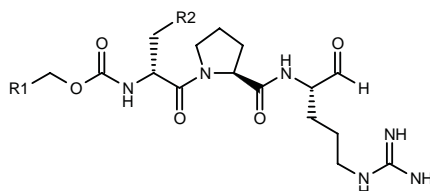
260076

Ethoxycarbonyl-D-(3-cyclobutyl)alanyl-L-prolyl-L-argininal



C21-H36-N6-O5; Mol wt: 452.55

ACTION – Antithrombotic agent that displays anticoagulant and platelet aggregation-inhibitory properties. Compound inhibits plasma clot-bound factor Xa and thrombin (IC_{50} = 0.70 and 0.39 μ M, respectively) and fibrin gel-bound thrombin (IC_{50} = 0.32 μ M), while showing only moderate antifibrinolytic activity. Peptide concentrations prolonging clotting time 2-fold compared to controls in the prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) tests were 1.15, 0.35 and 0.11 μ M, respectively, and it showed longer lasting oral anticoagulant and antiaggregant effects in rabbits compared to prior art related compounds. Other specifically claimed peptidyl-arginine aldehyde derivatives include the following:



Compound	R1	R2	Formula
261031	H	cyclobutyl	C ₂₀ H ₃₄ N ₆ O ₅
261032	Me	cyclopentyl	C ₂₂ H ₃₈ N ₆ O ₅
261033	H	cyclopentyl	C ₂₁ H ₃₈ N ₆ O ₅

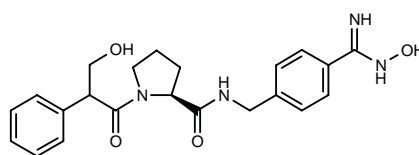
SOURCE – Gyógyszerkutató Intézet.

REFERENCES

1. Bajusz, S. et al. (Gyógyszerkutató Intézet KFT) *Anticoagulant peptidyl-arginine aldehyde derivs*. WO 9746576.

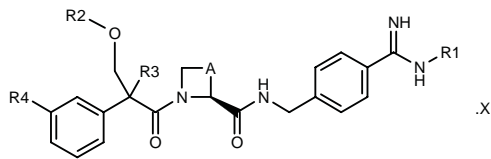
260077

N¹-Hydroxy-4-[1-(3-hydroxy-2-phenylpropionyl)-L-prolyl-aminomethyl]benzamidine



C22-H26-N4-O4; Mol wt: 410.47

ACTION – Anticoagulant and antithrombotic agent, a competitive inhibitor of trypsin-like serine proteases, particularly thrombin. Other compounds from this series of cyclic amino acid derivatives include the following:



Compound	R1	R2=R3	R4	A	X	Formula
260715	OH	H	OMe	-(CH2)2-		C ₂₂ H ₂₆ N ₄ O ₅
260716	CO ₂ CH ₂ Ph	H	OMe	-(CH ₂) ₂ -	acetate	C ₃₁ H ₃₄ N ₄ O ₆ .C ₂ H ₄ O ₂
260717	OH	H	OMe	-(CH ₂) ₂ -		C ₂₃ H ₂₈ N ₄ O ₅
260718	OCOEt	H	OMe	-(CH ₂) ₂ -		C ₂₆ H ₃₂ N ₄ O ₆
260719	OAc	H	OMe	-(CH ₂) ₂ -		C ₂₅ H ₃₀ N ₄ O ₆
260720	CO ₂ CH ₂ Ph	Me	H	-(CH ₂) ₂ -		C ₃₂ H ₃₆ N ₄ O ₅

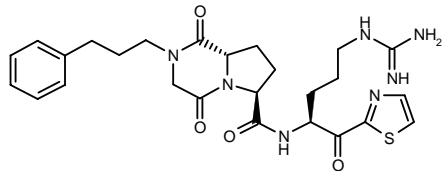
SOURCE – Astra.

REFERENCES

1. Gustafsson, D. and Nyström, J.-E. (Astra AB) *New amino acid derivs. and their use as thrombin inhibitors*. WO 9746577.

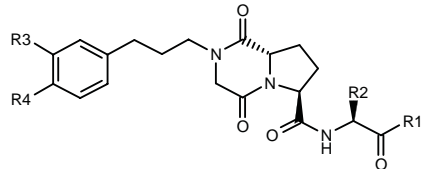
260137

[6*S*-[6α(*R**),8αα]]-*N*-[4-Guanidino-1-(thiazol-2-yl-carbonyl)butyl]-1,4-dioxo-2-(3-phenylpropyl)-perhydropyrrolo[1,2-*a*]pyrazine-6-carboxamide



C26-H33-N7-O4-S; Mol wt: 539.65

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of serine proteases such as thrombin ($K_i = 3$ nM), factor Xa ($IC_{50} = 30$ nM) and trypsin ($IC_{50} < 1$ nM). *In vivo*, it produced a > 3.3-fold shift in mean occlusion time in an FeCl₃-induced model of carotid arterial thrombosis in rats when given as an i.v. bolus (0.75 mg/kg) followed by an i.v. infusion (50 μg/kg/min). A representative compound from a series of pyrrolo[1,2-*a*]pyrazine-1,4-diones, wherein the following are also included:



Compound	R1	R2	R3=R4	Formula
260978	2-benzothiazolyl	1-[NH ₂ C(=NH)]-3(S)-Pip-CH ₂	Cl	C ₃₃ H ₃₇ Cl ₂ N ₇ O ₄ S
260979	1-Me-2-benzimidazolyl	3-[NH ₂ C(=NH)]-PhCH ₂	H	C ₃₅ H ₃₇ N ₇ O ₄
260980	2-benzothiazolyl	trans-4-NH ₂ -cyclohexyl	H	C ₃₂ H ₃₇ N ₅ O ₄ S

SOURCE – Warner-Lambert.

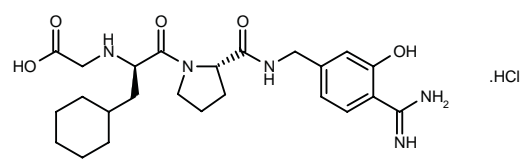
REFERENCES

1. Berryman, K.A. et al. (Warner-Lambert Co.) *Pyrrolo[1,2-*a*]pyrazine-1,4-dione serine protease inhibitors*. WO 9748706.

260157

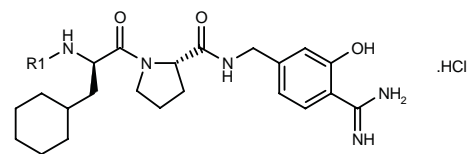
4-(Carboxymethyl-D-cyclohexylalanyl-L-prolylamino-methyl)-2-hydroxybenzamidinium hydrochloride

Carboxymethyl-D-cyclohexylalanyl-L-proline 4-amidino-3-hydroxybenzylamide hydrochloride



C24-H35-N5-O5.HCl; Mol wt: 510.03

ACTION – Anticoagulant and antithrombotic agent, a potent and selective thrombin inhibitor reported to exhibit high bioavailability following oral administration. Other specifically claimed compounds from this series of 2-hydroxybenzamidinium derivatives are:



Compound	R1	Formula
261448	H	C ₂₂ H ₃₄ ClN ₅ O ₃ .HCl
261449	SO ₂ Et	C ₂₄ H ₃₇ N ₅ O ₅ S.HCl

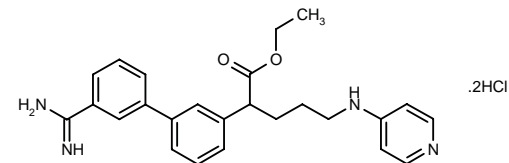
SOURCE – Lilly.

REFERENCES

1. Klimkowski, V.J. et al. (Eli Lilly & Co.) *Anticoagulant agents*. EP 816376, WO 9749404.

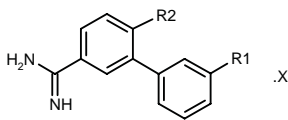
260507

2-(3'-Amidinobiphenyl-3-yl)-5-(4-pyridylamino)pentanoic acid ethyl ester dihydrochloride



C25-H28-N4-O2.2HCl; Mol wt: 489.44

ACTION – Anticoagulant and antithrombotic agent, a potent human factor Xa inhibitor ($IC_{50} = 0.069$ μM) with high selectivity over thrombin ($IC_{50} > 100$ μM). Other compounds from this series of biphenylamidinium derivatives include the following:



Compound	R1	R2	X	Formula
262187	4-Pyr-NHCH2CH2O	H	2HCl	C ₂₀ H ₂₀ N ₄ O.2HCl
262188	4-Pyr-NH(CH2)3S	H	2HCl	C ₂₁ H ₂₂ N ₄ S.2HCl
262189	4-Pyr-NH-(CH2)3CH(CO2H)	H	2HCl	C ₂₃ H ₂₄ N ₄ O ₂ .2HCl
262190	4-Pyr-NHCH2-CH2CH(CO2Et)	H	2HCl	C ₂₄ H ₂₆ N ₄ O ₂ .2HCl
262191	(E)-4-Pyr-NH-CH2CH=CH	H	2HCl	C ₂₁ H ₂₀ N ₄ .2HCl
262192	4-Pyr-NH(CH2)3	H	2HCl	C ₂₁ H ₂₂ N ₄ .2HCl
262193	4-Pyr-NH(CH2)4	H	2HCl	C ₂₂ H ₂₄ N ₄ .2HCl
262194	4-Pyr-NH(CH2)3	CH2OH	2CF3CO2H	C ₂₂ H ₂₄ N ₄ O .2C ₂ HF ₃ O ₂
262195	(E)-5-isindoliny- -CH=CHCH2(CO2Et)	H	2CF3CO2H	C ₂₈ H ₂₉ N ₃ O ₂ .2C ₂ HF ₃ O ₂
262196	(E)-5-isindoliny- -CH=CHCH2CH(CO2H)	H	2CF3CO2H	C ₂₈ H ₂₆ N ₃ O ₂ .2C ₂ HF ₃ O ₂

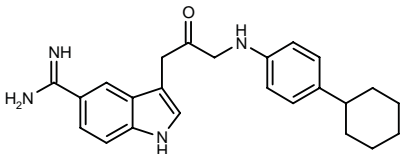
SOURCE – Banyu.

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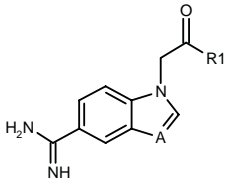
261201

3-[3-(4-Cyclohexylphenylamino)-2-oxopropyl]-1*H*-indole-5-carboxamidine

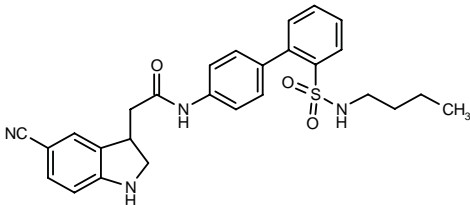


C24-H28-N4-O; Mol wt: 388.51

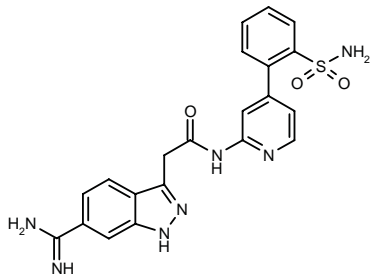
ACTION – Anticoagulant and antithrombotic agent, an inhibitor of thrombin and factor Xa. Other specifically claimed compounds from this series of amidinoindoles, amidinoazoles and analogs thereof include the following:



Compound	R1	A	Formula
261715	4-Ph-Ph	N	C ₂₂ H ₁₈ N ₄ O
261716	4-(PhCH2)-1-Pip	CH	C ₂₃ H ₂₆ N ₄ O



261713: C27-H28-N4-O3-S



261714: C21-H19-N7-O3-S

SOURCE – DuPont Merck.

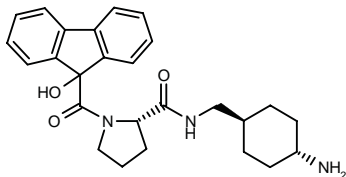
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1. Dominguez, C. et al. (The Du Pont Merck Pharm. Co.) *Amidinoindoles, amidinoazoles, and analogs thereof as inhibitors of factor Xa and of thrombin.* WO 9801428.

L-372460

260578

1-(9-Hydroxy-9*H*-fluoren-9-ylcarbonyl)-L-proline *trans*-4-aminocyclohexylmethylamide



C26-H31-N3-O3; Mol wt: 433.55

ACTION – Potent thrombin inhibitor (IC₅₀ = 4 nM, K_i = 1.5 nM) with good selectivity relative to trypsin (K_i = 860 nM) and several other serine proteases (K_i = 20 μM or more for plasmin, tPA, activated protein C, plasma kallikrein and chymotrypsin). It completely prevented occlusion in a rat model of FeCl₃-induced thrombosis at a dose of 10 μg/kg/min. Although it showed poor oral absorption in rats, it exhibited high oral bioavailability in dogs (74%) and was also orally bioavailable in cynomolgus monkeys (39%).

SOURCE – Merck & Co.

REFERENCES

1. Lumma, W.C. et al. (Merck & Co., Inc.) *Thrombin inhibitors.* JP 98503204, US 5510369, WO 9603374.

2. Brady, S.F. et al. *Discovery and development of the novel potent orally active thrombin inhibitor N-(9-hydroxy-9-fluorencarboxy)prolyl trans-4-aminocyclohexylmethyl amide (L-372,460): Coapplication of structure-based design and rapid multiple analogue synthesis on solid support.* J Med Chem 1998, 41(3): 401.

TSETSE THROMBIN INHIBITOR

259009

Polypeptide with a molecular weight of 3520 Daltons

ACTION – Antithrombotic polypeptide that acts by inhibiting thrombin, isolated and purified from salivary gland extracts of the tsetse fly *Glossina morsitans morsitans*. It exhibits potent activity in inhibiting thrombin-induced platelet aggregation.

SOURCE – Yale Univ., New Haven, CT (US).

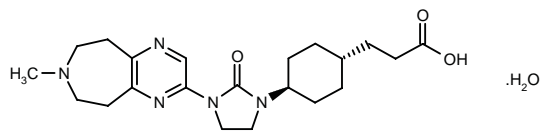
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ANTIPLATELET THERAPY

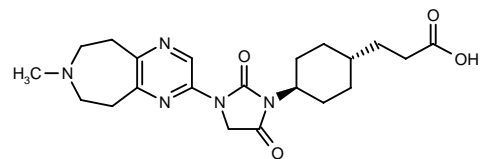
260135

trans-3-[4-[3-(7-Methyl-6,7,8,9-tetrahydro-5*H*-pyrazino-[2,3-*d*]azepin-2-yl)-2-oxoimidazolidin-1-yl]cyclohexyl]-propionic acid hydrate



C21-H31-N5-O3.H2-O; Mol wt: 419.52

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 11 nM against [³H]-BIBU-52 binding in human platelets) proven to inhibit collagen-induced aggregation of human platelets (IC₅₀ = 100 nM). Another specifically claimed compound from this series of benzazepine derivatives is:



260965: C21-H29-N5-O4

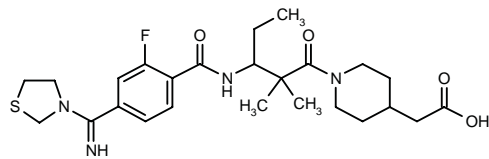
SOURCE – Boehringer Ingelheim.

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1. Himmelsbach, F. et al. (Dr. Karl Thomae GmbH) *Benzazepine derivs., medicaments containing these cpds. and process for their production*. WO 9748702.

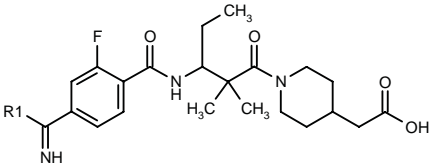
260181

2-[1-[3-[2-Fluoro-4-(thiazolidin-3-yl)carbonimidoyl]-benzamido]-2,2-dimethylpentanoyl]piperidin-4-yl]acetic acid



C25-H35-F-N4-O4-S; Mol wt: 506.63

ACTION – Platelet aggregation inhibitor and anti-thrombotic agent, a fibrinogen (gpIIb/IIIa) receptor antagonist with an IC₅₀ of 0.043 μM when tested *in vitro* for its inhibitory effect against collagen-induced human platelet aggregation. Other representative compounds include the following:



Compound	R1	Formula
261326	1-pyrrolidinyl	C ₂₆ H ₃₇ FN ₄ O ₄
261327	4-OH-1-Pip	C ₂₇ H ₃₉ FN ₄ O ₅
261328	4-Me-1-Piz	C ₂₇ H ₄₀ FN ₅ O ₄
261329	4-Ph-1-Piz	C ₃₂ H ₄₂ FN ₅ O ₄
261330	4-(4-F-Ph)-1-Piz	C ₃₂ H ₄₁ F ₂ N ₅ O ₄

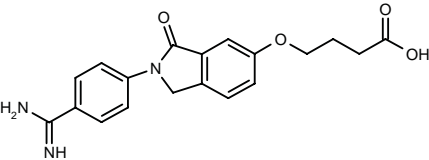
SOURCE – Nippon Steel.

REFERENCES

1. Hayashi, Y. et al. (Nippon Steel Corp.) *Fibrinogen receptor antagonists and medicinal preparations containing the same as the active ingredient*. JP 98017550, WO 9749682.

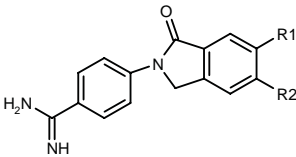
260528

4-[2-(4-Amidinophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-yl]oxy]butyric acid



C19-H19-N3-O4; Mol wt: 353.38

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist. It inhibited collagen-induced aggregation of human platelet-rich plasma (PRP) with an IC₅₀ value of 46 nM. Other related compounds include the following:



Compound	R1	R2	Formula
261473	O(CH2)4CO2H	H	C ₂₀ H ₂₁ N ₃ O ₄
261474	H	O(CH2)3CO2H	C ₁₉ H ₁₉ N ₃ O ₄
261475	H	O(CH2)4CO2H	C ₂₀ H ₂₁ N ₃ O ₄

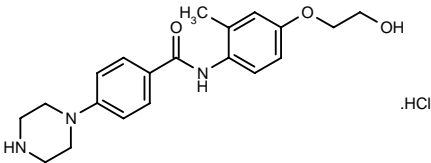
SOURCE – Nippon Steel.

REFERENCES

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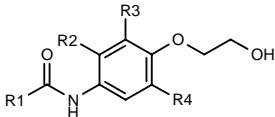
261151

N-[4-(2-Hydroxyethoxy)-2-methylphenyl]-4-(1-piperazinyl)benzamide hydrochloride



C20-H25-N3-O3.HCl; Mol wt: 391.90

ACTION – Platelet aggregation inhibitor, a prodrug of a known fibrinogen (gpIIb/IIIa) receptor antagonist that is metabolized *in vivo* to release the active acid species. Other specifically claimed compounds from this series of alcohol prodrugs of fibrinogen antagonists include the following:



Compound	R1	R2	R3	R4	Formula
261417	4-(1-Piz)-Ph	H	H	H	C ₁₉ H ₂₄ ClN ₃ O ₃
261418	4-(1-Piz)-Ph	H	H	SO ₂ Me	C ₂₀ H ₂₅ N ₃ O ₅ S
261419	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-7-yl	Me	H	H	C ₂₁ H ₂₃ N ₃ O ₃
261420	4-(1-Piz)-Ph	Me	Br	Br	C ₂₀ H ₂₃ Br ₂ N ₃ O ₃
261421	1-(4-Pyr)-4-Pip	Me	H	H	C ₂₀ H ₂₅ N ₃ O ₃

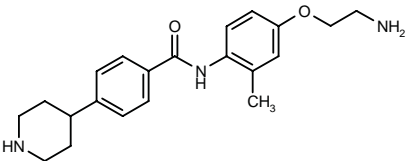
SOURCE – Merck & Co.

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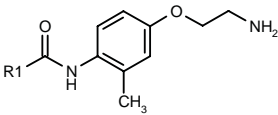
261155

N-[4-(2-Aminoethoxy)-2-methylphenyl]-4-(4-piperidyl)-benzamide

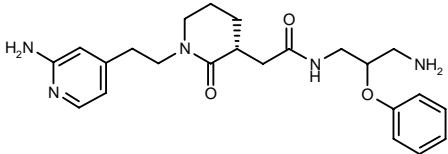


C21-H27-N3-O2; Mol wt: 353.46

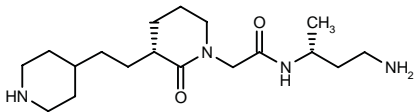
ACTION – Antithrombotic agent, an orally active prodrug of a fibrinogen (gpIIb/IIIa) receptor antagonist that is metabolized *in vivo* to the active acid. Other specifically claimed compounds from this series of alcohol prodrugs include the following:



Compound	R1	Formula
261424	4-(1-Piz)-Ph	C ₂₀ H ₂₆ N ₄ O ₂
261425	4-(2-NH2-4-Pyr)-Ph	C ₂₁ H ₂₂ N ₄ O ₂
261426	2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-7-yl	C ₂₁ H ₂₄ N ₄ O ₂



261427: C23-H31-N5-O3



261428: C18-H34-N4-O2

SOURCE – Merck & Co.

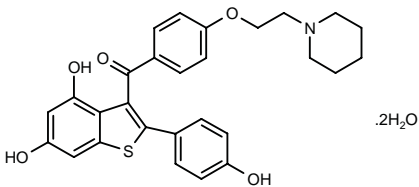
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THROMBOLYTICS

260875

1-[4,6-Dihydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-1-[4-[2-(1-piperidyl)ethoxy]phenyl]methanone dihydrate



C28-H27-N-O5-S.2H2O; Mol wt: 525.62

ACTION – A potent inhibitor of plasminogen activator inhibitor-1 (PAI-1) proven to significantly reduce the induction of PAI-1 by IL-1 from human umbilical vein endothelial cells (HUVEC) at 1 nM. Potentially useful for reducing cardiovascular events by enhancing fibrinolysis, as well as for thrombotic disorders, sepsis/septic shock and metastasis.

SOURCE – Lilly.

REFERENCES

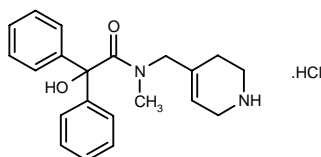
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RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

259208

2-Hydroxy-*N*-methyl-2,2-diphenyl-*N*-(1,2,3,6-tetrahydropyridin-4-ylmethyl)acetamide hydrochloride



C21-H24-N2-O2.HCl; Mol wt: 372.89

ACTION – Anticholinergic agent for the treatment of pollakuria and urinary incontinence, proven to inhibit urinary bladder contractions in rats ($ED_{30} = 0.0056$ mg/kg i.v.).

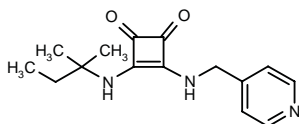
SOURCE – Fujisawa.

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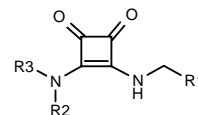
260122

3-(1,1-Dimethylpropylamino)-4-(pyridin-4-ylmethylamino)-3-cyclobutene-1,2-dione



C15-H19-N3-O2; Mol wt: 273.33

ACTION – Smooth muscle relaxant that acts by activating potassium channels. It inhibited KCl-induced contractions of isolated rat bladder strips with an IC_{50} value of 0.42 ± 0.06 μ M and produced an $8 \pm 4\%$ reduction in the total number of contractions when administered at 10 mg/kg p.o. to rats with hypertrophied bladders. Potentially useful for the treatment of disorders associated with smooth muscle contraction, particularly urinary incontinence and irritable bowel syndrome. Other specifically claimed compounds from this series of heterocyclylmethylamino derivatives of cyclobutene-3,4-diones include the following:



Compound	R1	R2	R3	Formula
260927	3-Pyr	C(Me)2Et	H	C ₁₅ H ₁₉ N ₃ O ₂
260928	2-Pyr	C(Me)2Et	H	C ₁₅ H ₁₉ N ₃ O ₂
260929	4-Pyr	t-Bu	H	C ₁₄ H ₁₇ N ₃ O ₂
260930	3-Pyr	t-Bu	H	C ₁₄ H ₁₇ N ₃ O ₂
260931	2-Pyr	t-Bu	H	C ₁₄ H ₁₇ N ₃ O ₂
260932	4-Pyr	i-Pr	Me	C ₁₄ H ₁₇ N ₃ O ₂
260933	5-NO ₂ -2-benzofuryl	t-BuCH(Me)	H	C ₁₉ H ₂₁ N ₃ O ₅
260934	5-NO ₂ -2-benzofuryl	C(Me)2Et	H	C ₁₈ H ₁₉ N ₃ O ₅
260935	5-NO ₂ -2-benzofuryl	t-Bu	H	C ₁₇ H ₁₇ N ₃ O ₅
260936	5-CN-2-benzofuyl	C(Me)2Et	H	C ₁₉ H ₁₉ N ₃ O ₃
260937	5-CN-2-benzofuyl	t-BuCH(Me)	H	C ₂₀ H ₂₁ N ₃ O ₃
260938	5-CN-2-benzofuyl	t-Bu	H	C ₁₈ H ₁₇ N ₃ O ₃
260939	5-CN-2-benzofuyl	C(Me)2CH2Ph	H	C ₂₄ H ₂₁ N ₃ O ₃
260940	4-Pyr	t-BuCH(Me)	H	C ₁₆ H ₂₁ N ₃ O ₂
260941	3-Cl-5-CN-2-benzofuryl	C(Me)2Et	H	C ₁₉ H ₁₈ ClN ₃ O ₃

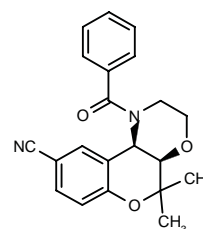
SOURCE – American Home Products.

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261120

(–)-(4*aR*,10*bR*)-1-Benzoyl-5,5-dimethyl-1,2,3,4*a*,5,10*b*-hexahydro[1]benzopyran[3,4-*b*][1,4]oxazine-9-carbonitrile



C21-H20-N2-O3; Mol wt: 348.40

ACTION – Bladder-selective potassium channel opener with an IC_{50} of 8.15 ± 1.9 μ M for inhibition of KCl-induced contractions in isolated rat detrusor strips versus an IC_{50} of 34.5 ± 0.71 μ M for inhibition of spontaneous contractions in rat portal vein. A lead compound from a series of optically active tetrahydro-oxazino[2,3-*c*]-benzopyran derivatives.

Such compounds are expected to be useful in the treatment of urinary incontinence.

SOURCE – Natl. Taiwan Univ., Taipei (TW).

REFERENCES

1. Cheng, C.-Y. et al. *Synthesis of 2,3,4*a*,11*b*-tetrahydro-oxazino[2,3-*c*]benzopyran-9-carbonitriles as ATP-sensitive potassium channel openers.* Bioorg Med Chem Lett 1998, 8(5): 463.

TREATMENT OF RENAL DISEASES

SEVELAMER

Prop INN

222461

Allylamine polymer with 1-chloro-2,3-epoxypropane

PB-94

RenaGel®

ACTION – Nonabsorbed phosphate binder hydrogel that binds to and removes dietary phosphorus in the gastrointestinal tract without being absorbed into the bloodstream, for use in the control of elevated phosphate levels in patients with chronic renal failure. It is currently under review at the FDA.

SOURCES – Chugai; GelTex; Genzyme; Kirin Brewery; RenaGel (50/50 joint venture of Geltex and Genzyme).

REFERENCES

- Burke, S.K. et al. *RenaGel®*, a novel calcium- and aluminium-free phosphate binder, inhibits phosphate absorption in normal volunteers. *Nephrol Dialysis Transplant* 1997, 12(8): 1640.
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- Chugai Pharmaceutical develops a hyperphosphatemia agent with an U.S. bioventure company*. *Nikkei Sangyo Shinbun* 1995, October 13.
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- GelTex announces positive preliminary phase IIc results for RenaGel® phosphate binder. Company also receives second patent on cholesterol reducing polymers*. *GelTex Pharmaceuticals, Inc. Press Release* 1997, April 8.
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- GelTex Pharmaceuticals reports positive preliminary phase III clinical results for RenaGel® phosphate binder*. *GelTex Pharmaceuticals, Inc. Press Release* 1997, January 8.
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- GelTex Pharmaceuticals reports positive results from second phase III clinical trial for RenaGel® phosphate binder. Comparative trial affirms key advantage of phosphate control without calcium elevation*. *GelTex Pharmaceuticals, Inc. Press Release* 1997, March 10.
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- GelTex submits NDA for RenaGel*. *Prous Science Daily Essentials* November 4, 1997.
- Joint venture formed to market RenaGel*. *Prous Science Daily Essentials* June 19, 1997.

18. *Kirin Brewery will collaborate with Chugai on PB-94 development*. *Prous Science Daily Essentials* March 2, 1998.

19. *Positive phase III results for GelTex's RenaGel*. *Prous Science Daily Essentials* March 12, 1997.

20. *Positive phase III trial results reported for phosphate binder*. *Prous Science Daily Essentials* January 9, 1997.

21. *Proposed international nonproprietary names (Prop. INN): List 77*. *WHO Drug Inform* 1997, 11(2): 101.

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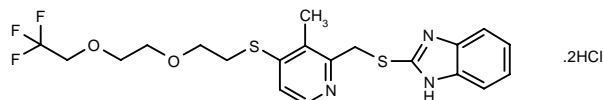
23. *RenaGel with and without calcium effective in ESRD*. *Prous Science Daily Essentials* November 10, 1997.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

257729

2-[3-Methyl-4-[2-[2-(2,2,2-trifluoroethoxy)ethoxy]-ethylsulfanyl]pyridin-2-ylmethylsulfanyl]benzimidazole dihydrochloride



C20-H22-F3-N3-O2-S2.2HCl; Mol wt: 530.45

ACTION – Gastric antisecretory and antiulcer agent active *in vitro* against *Helicobacter pylori* (MIC = 0.1 µg/ml) and *in vivo* in rats, completely eliminating *H. pylori* when administered orally twice daily for 14 days. No deaths were observed after doses of 50 mg/kg i.v. or 1000 mg/kg p.o. in mice.

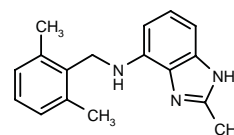
SOURCE – Yoshitomi.

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260105

N-(2,6-Dimethylbenzyl)-*N*-(2-methylbenzimidazol-4-yl)amine



C17-H19-N3; Mol wt: 265.36

TREATMENT OF RENAL DISEASES

SEVELAMER

Prop INN

222461

Allylamine polymer with 1-chloro-2,3-epoxypropane

PB-94

RenaGel®

ACTION – Nonabsorbed phosphate binder hydrogel that binds to and removes dietary phosphorus in the gastrointestinal tract without being absorbed into the bloodstream, for use in the control of elevated phosphate levels in patients with chronic renal failure. It is currently under review at the FDA.

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- GelTex Pharmaceuticals reports positive preliminary phase III clinical results for RenaGel phosphate binder*. *Dialysis Transplant* 1997, 26(3): 126.
- GelTex Pharmaceuticals reports positive results from second phase III clinical trial for RenaGel® phosphate binder. Comparative trial affirms key advantage of phosphate control without calcium elevation*. *GelTex Pharmaceuticals, Inc. Press Release* 1997, March 10.
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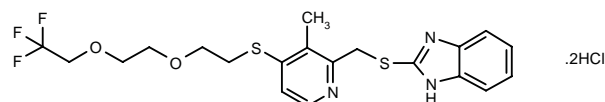
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

257729

2-[3-Methyl-4-[2-[2-(2,2,2-trifluoroethoxy)ethoxy]-ethylsulfanyl]pyridin-2-ylmethylsulfanyl]benzimidazole dihydrochloride



C20-H22-F3-N3-O2-S2.2HCl; Mol wt: 530.45

ACTION – Gastric antisecretory and antiulcer agent active *in vitro* against *Helicobacter pylori* (MIC = 0.1 µg/ml) and *in vivo* in rats, completely eliminating *H. pylori* when administered orally twice daily for 14 days. No deaths were observed after doses of 50 mg/kg i.v. or 1000 mg/kg p.o. in mice.

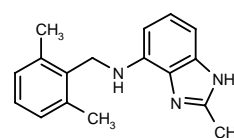
SOURCE – Yoshitomi.

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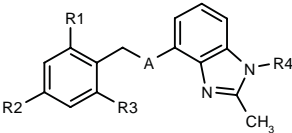
260105

N-(2,6-Dimethylbenzyl)-*N*-(2-methylbenzimidazol-4-yl)amine



C17-H19-N3; Mol wt: 265.36

ACTION – Gastric antisecretory agent that acts by inhibiting H⁺/K⁺-ATPase and exhibits better inhibitory effect against acid secretion *in vitro* in isolated rabbit gastric glands than prior art related compounds. Other specifically claimed benzimidazole derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
260782	Me	H	Me	H	O	C ₁₇ H ₁₈ N ₂ O
260783	Me	F	Me	H	NH	C ₁₇ H ₁₈ FN ₃
260784	Me	F	Me	H	O	C ₁₇ H ₁₇ FN ₂ O
260785	Me	H	Me	Me	NH	C ₁₈ H ₂₁ N ₃
260786	Et	H	Me	H	NH	C ₁₈ H ₂₁ N ₃
260787	Et	H	Et	H	NH	C ₁₉ H ₂₃ N ₃
260788	Me	F	Me	Me	NH	C ₁₈ H ₂₀ FN ₃
260789	Me	F	Me	Me	O	C ₁₈ H ₁₉ FN ₂ O

SOURCE – Astra.

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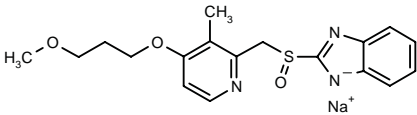
RABEPRAZOLE SODIUM

Rec INN; USAN

143151

2-[4-(3-Methoxypropoxy)-3-methylpyridin-2-ylmethylsulfanyl]benzimidazole 1-sodium salt

E-3810⁺
LY-307640
Pariprazole sodium



C18-H20-N3-Na-O3-S; Mol wt: 381.42

ACTION – Proton pump inhibitor.

INDICATION – Treatment of gastric and duodenal ulcers and gastroesophageal reflux disease.

PRESENTATION – Tablets, 10 and 20 mg.

PROPRIETARY NAME – *Pariet* (JP).

SOURCE – Eisai.

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2. Dammann, H.G. et al. *Rabeprazole effectively inhibits 24 hr H⁺ activity and nocturnal acid secretion in healthy subjects.* Amer J Gastroenterol 1996, 91(9): Abst 647.

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13. Mano, N. et al. *Plasma direct injection high-performance liquid chromatographic method for simultaneously determining E3810 enantiomers and their metabolites by using flavoprotein-conjugated column.* J Pharm Sci 1996, 85(9): 903.

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15. Nochi, S. et al. *Preparation and absolute configurations of optical isomers of sodium 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfanyl]-1H-benzimidazole (E3810).* Chem Pharm Bull 1996, 44(10): 1853.

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22. Takakuwa, S. et al. *Enantioselective pharmacokinetics of E3810, a new anti-ulcer agent, in dogs and rats.* 7th North Amer ISSX Meet (Oct 20-24, San Diego) 1996, Abst 346.

23. Thjodleifsson, B. et al. *Rabeprazole sodium 20 mg once daily is similar to omeprazole 20 mg once daily in the treatment of erosive or ulcerative GERD.* Digest Dis Week (May 10-16, Washington DC) 1997, Abst 439.

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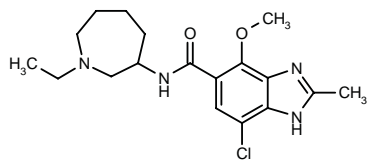
MONOGRAPH – Prous, J. and Castañer, J. *E-3810.* Drugs Fut 1991, 16(1): 19.

*Drug Data Rep 1990, 12(7): 565.

TREATMENT OF DISORDERS OF
GASTRIC EMPTYING

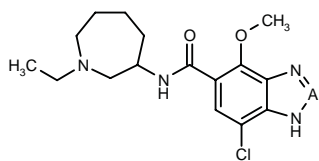
258447

7-Chloro-*N*-(1-ethylperhydrozepin-3-yl)-4-methoxy-2-methyl-1*H*-benzimidazole-5-carboxamide



C18-H25-Cl-N4-O2; Mol wt: 364.87

ACTION – Gastrointestinal prokinetic and antiemetic agent, as shown by its ability to inhibit apomorphine-induced emesis in dogs (88% inhibition at 1.0 mg/kg p.o. vs. 86% for metoclopramide at the same dose) and to promote gastric emptying in rats (43% at 3 mg/kg p.o. vs. 31% for metoclopramide at 10 mg/kg p.o.). Other compounds from this series of azacycloalkane carboxamides include the following:



Compound	A	Isomer	Formula
261010	N		C ₁₆ H ₂₂ ClN ₅ O ₂
261011	N	R	C ₁₆ H ₂₂ ClN ₅ O ₂
261012	C(Me)	R	C ₁₈ H ₂₅ ClN ₄ O ₂

SOURCE – Dainippon.

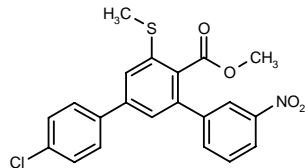
REFERENCES

1. Kato, S. et al. (Dainippon Pharm. Co., Ltd.) *N*-(1-Substd.-azacycloalkan-3-yl)carboxamide derivs. and medicinal compsns. containing them. JP 97301972.

TREATMENT OF LIVER AND BILIARY
TRACT DISORDERS

261121

4-Chloro-5'-(methylsulfanyl)-3''-nitro[1,1':3',1''-terphenyl]-4'-carboxylic acid methyl ester



C21-H16-Cl-N-O4-S; Mol wt: 413.87

ACTIONS – Hepatoprotective agent proven effective against thioacetamide-induced hepatic injury in rats; title compound reduced serum enzyme parameters indicative of hepatic toxicity such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT) and alkaline phosphatase (ALP) (70, 64 and 60% protection, respectively).

SOURCE – Central Drug Res. Inst., Lucknow (IN).

REFERENCES

1. Ram, V.J. et al. *Functionalized 1,3-teraryls as a new class of hepatoprotectants: Part V. Bioorg Med Chem Lett* 1998, 8(5): 469.

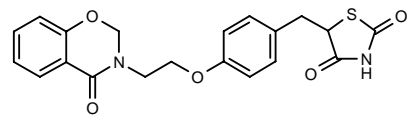
2. Ram, V.-J. and Goel, A. *Ring transformation reactions. Part IV. 6-Aryl-3-methoxycarbonyl-4-methylthio-2H-pyran-2-one. A novel synthon for the synthesis of 1,3-terphenyls from aryl ketones. Tetrahedron Lett* 1996, 37(1): 93.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

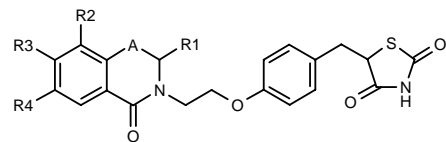
257481

3-[2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenoxy]ethyl]-3,4-dihydro-2*H*-1,3-benzoxazin-4-one



C20-H18-N2-O5-S; Mol wt: 398.43

ACTION – Antidiabetic agent with marked blood glucose-lowering activity (65.8% at 9.8 mg/kg/day in the diet for 4 days) in KK-A^Y/TaJcl mice, as well as good plasma insulin- and triglyceride-lowering activity (67.4 and 75.0%, respectively, at the same dose level); the respective values for troglitazone were 50.8, 69.2 and 44.0% at a dose of 183.5 mg/kg/day. Within this series of benzoazine derivatives, the following are also included:

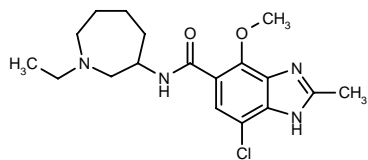


Compound	R1	R2	R3	R4	A	Formula
260740	Me	H	H	H	O	C ₂₁ H ₂₀ N ₂ O ₅ S
260741	H	H	Me	H	O	C ₂₁ H ₂₀ N ₂ O ₅ S
260742	H	H	H	OMe	O	C ₂₁ H ₂₀ N ₂ O ₆ S
260743	H	OMe	H	H	O	C ₂₁ H ₂₀ N ₂ O ₆ S
260744	H	H	H	Cl	O	C ₂₀ H ₁₇ ClN ₂ O ₅ S
260745	H	H	OMe	H	O	C ₂₁ H ₂₀ N ₂ O ₆ S
260746	H	H	H	H	N(Me)	C ₂₁ H ₂₁ N ₃ O ₄ S

TREATMENT OF DISORDERS OF
GASTRIC EMPTYING

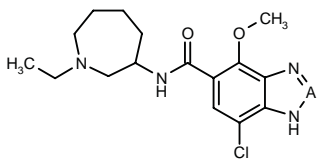
258447

7-Chloro-*N*-(1-ethylperhydrozepin-3-yl)-4-methoxy-2-methyl-1*H*-benzimidazole-5-carboxamide



C18-H25-Cl-N4-O2; Mol wt: 364.87

ACTION – Gastrointestinal prokinetic and antiemetic agent, as shown by its ability to inhibit apomorphine-induced emesis in dogs (88% inhibition at 1.0 mg/kg p.o. vs. 86% for metoclopramide at the same dose) and to promote gastric emptying in rats (43% at 3 mg/kg p.o. vs. 31% for metoclopramide at 10 mg/kg p.o.). Other compounds from this series of azacycloalkane carboxamides include the following:



Compound	A	Isomer	Formula
261010	N		C ₁₆ H ₂₂ ClN ₅ O ₂
261011	N	R	C ₁₆ H ₂₂ ClN ₅ O ₂
261012	C(Me)	R	C ₁₈ H ₂₅ ClN ₄ O ₂

SOURCE – Dainippon.

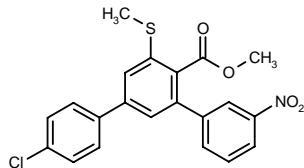
REFERENCES

1. Kato, S. et al. (Dainippon Pharm. Co., Ltd.) *N*-(1-Substd.-azacycloalkan-3-yl)carboxamide derivs. and medicinal compsns. containing them. JP 97301972.

TREATMENT OF LIVER AND BILIARY
TRACT DISORDERS

261121

4-Chloro-5'-(methylsulfanyl)-3''-nitro[1,1':3',1''-terphenyl]-4'-carboxylic acid methyl ester



C21-H16-Cl-N-O4-S; Mol wt: 413.87

ACTIONS – Hepatoprotective agent proven effective against thioacetamide-induced hepatic injury in rats; title compound reduced serum enzyme parameters indicative of hepatic toxicity such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT) and alkaline phosphatase (ALP) (70, 64 and 60% protection, respectively).

SOURCE – Central Drug Res. Inst., Lucknow (IN).

REFERENCES

1. Ram, V.J. et al. *Functionalized 1,3-teraryls as a new class of hepatoprotectants: Part V. Bioorg Med Chem Lett* 1998, 8(5): 469.

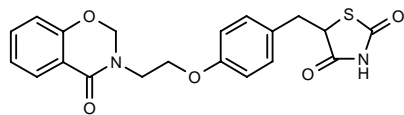
2. Ram, V.-J. and Goel, A. *Ring transformation reactions. Part IV. 6-Aryl-3-methoxycarbonyl-4-methylthio-2H-pyran-2-one. A novel synthon for the synthesis of 1,3-terphenyls from aryl ketones. Tetrahedron Lett* 1996, 37(1): 93.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

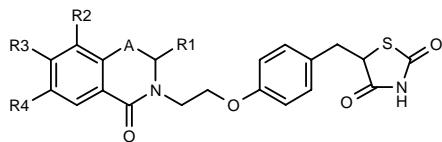
257481

3-[2-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenoxy]ethyl]-3,4-dihydro-2*H*-1,3-benzoxazin-4-one



C20-H18-N2-O5-S; Mol wt: 398.43

ACTION – Antidiabetic agent with marked blood glucose-lowering activity (65.8% at 9.8 mg/kg/day in the diet for 4 days) in KK-A^Y/TaJcl mice, as well as good plasma insulin- and triglyceride-lowering activity (67.4 and 75.0%, respectively, at the same dose level); the respective values for troglitazone were 50.8, 69.2 and 44.0% at a dose of 183.5 mg/kg/day. Within this series of benzoazine derivatives, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
260740	Me	H	H	H	O	C ₂₁ H ₂₀ N ₂ O ₅ S
260741	H	H	Me	H	O	C ₂₁ H ₂₀ N ₂ O ₅ S
260742	H	H	H	OMe	O	C ₂₁ H ₂₀ N ₂ O ₆ S
260743	H	OMe	H	H	O	C ₂₁ H ₂₀ N ₂ O ₆ S
260744	H	H	H	Cl	O	C ₂₀ H ₁₇ ClN ₂ O ₅ S
260745	H	H	OMe	H	O	C ₂₁ H ₂₀ N ₂ O ₆ S
260746	H	H	H	H	N(Me)	C ₂₁ H ₂₁ N ₃ O ₄ S

SOURCE – SS Pharm.

REFERENCES

1. Nagao, Y. et al. (SS Pharm. Co., Ltd.) *Benzoazine derivs. or salts thereof, and medicinal containing the same*. JP 97268189, US 5710152.

260081

Histidyl-seryl-aspartyl-glycyl-threonyl-phenylalanyl-threonyl-seryl-aspartyl-leucyl-seryl-lysyl-glutaminylnorleucyl-glutamyl-glutamyl-glutamyl-alanyl-valyl-arginyl-leucyl-phenylalanyl-isoleucyl-glutamyl-tryptophanyl-leucyl-lysyl-asparaginyll-glycyl-tyrosine

C158-H238-N40-O51; Mol wt: 3513.86

ACTION – Exendin analog for the treatment of diabetes that stimulates insulin secretion and interacts with the glucagon-like peptide-1 (GLP-1) receptor.

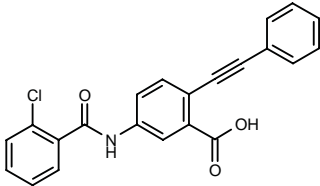
SOURCE – Boehringer Mannheim.

REFERENCES

1. Hoffmann, E. et al. (Boehringer Mannheim GmbH) *Exendin analogues, processes for their preparation and medicaments containing them*. WO 9746584.

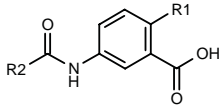
260846

5-(2-Chlorobenzamido)-2-(phenylethynyl)benzoic acid



C22-H14-Cl-N-O3; Mol wt: 375.81

ACTION – Agent for the treatment of type II diabetes that acts by inhibiting hepatic glucose-6-phosphatase activity (100% inhibition at 12.5 µM in rat hepatic microsomes), thus resulting in reduced glucose production in the liver. Compound is reported to possess improved bioavailability over previously known inhibitors. Other compounds from this series of substituted benzoic acid derivatives include the following:



Compound	R1	R2	Formula
261800	Ph-ethynylene	3-MeO-Ph	C ₂₃ H ₁₇ NO ₄
261801	Ph-ethynylene	3-CN-Ph	C ₂₃ H ₁₄ N ₂ O ₃
261802	Ph-ethynylene	3-F-Ph	C ₂₂ H ₁₄ FNO ₃
261803	4-Me-Ph-ethynylene	i-Pr	C ₂₀ H ₁₉ NO ₃
261890	6-MeO-2-Naph	2-thienyl	C ₂₃ H ₁₇ NO ₄ S

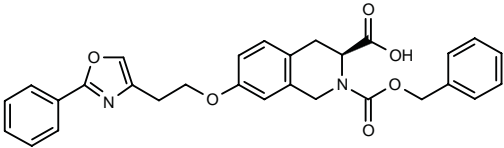
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Hemmerle, H. et al. (Hoechst AG) *Benzoic acid derivs., process for their preparation and their use for the treatment of diseases*. EP 816329.

261156

2-(Benzyloxycarbonyl)-7-[2-(2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid



C29-H26-N2-O6; Mol wt: 498.53

ACTION – Hypoglycemic and hypolipidemic agent proven to reduce serum glucose levels (32% of baseline values) and serum triglycerides (from 4 mmol/ml in controls to 2.5 mmol/ml) in obese-diabetic viable yellow (A^{vy}) mice when administered mixed with food at a concentration of 0.03% for 14 days.

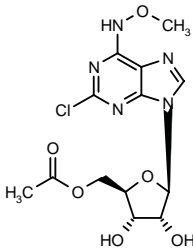
SOURCE – Lilly.

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1. Dominianni, S.J. and Gritton, W.H. (Eli Lilly & Co.) *Hypoglycemic and hypolipidemic cpds*. WO 9800403.

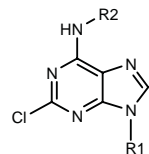
261212

5'-O-Acetyl-2-chloro-*N*⁶-methoxyadenosine

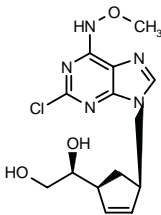


C13-H16-Cl-N5-O6; Mol wt: 373.75

ACTION – Agent for the treatment of inflammation, arthritis, type I and II diabetes, autoimmune diseases, multiple sclerosis, stroke, osteoporosis, septic shock and menstrual complications, preferably type II diabetes, with potent binding affinity for adenosine receptors; it modulates cAMP and acts as an inhibitor of cytokines such as tumor necrosis factor-α (TNF-α). Other specifically claimed compounds from this series of adenine derivatives include the following:



Compound	R1	R2	Formula
261742	5-O-Ac-β-D-ribofuranosyl	i-BuO	C ₁₆ H ₂₂ ClN ₅ O ₆
261743	5-O-Ac-β-D-ribofuranosyl	OCH ₂ CO ₂ Me	C ₁₅ H ₁₈ ClN ₅ O ₈
261744	5-O-Ac-2-deoxy-α-D-ribofuranosyl	OMe	C ₁₃ H ₁₆ ClN ₅ O ₅
261745	5-O-Ac-2,3-didehydro-2,3-dideoxy-β-D-ribofuranosyl	OMe	C ₁₃ H ₁₄ ClN ₅ O ₄
261746	4-(3-isoxazolyl)-β-D-erythrofuransyl	3-I-PhCH ₂	C ₁₉ H ₁₆ ClIN ₆ O ₄



261747: C13-H16-Cl-N5-O3

SOURCE – Novo Nordisk.

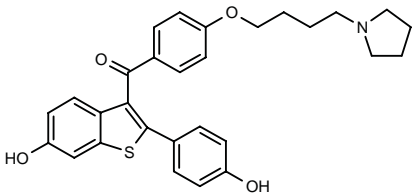
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1. Knutsen, L. et al. (Novo Nordisk A/S) *Novel N-alkoxyadenine derivs. acting as cytokine inhibitors*. WO 9801459.

TREATMENT OF GYNECOLOGICAL DISORDERS

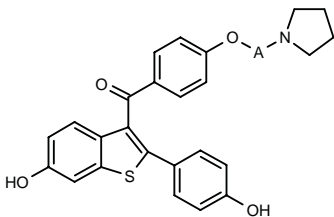
260852

1-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-1-[4-[4-(1-pyrrolidinyl)butoxy]phenyl]methanone



C29-H29-N-O4-S; Mol wt: 487.61

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders, hyperlipidemia and estrogen-dependent cancers, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 1.0 and 10 mg/kg/day p.o., while increasing uterine weight to a lesser extent than 17α-ethinylestradiol at 0.1 mg/kg/day; at these doses, compound was shown to produce much lower increases in uterus eosinophil infiltration than 17α-ethinylestradiol. A representative compound from a series of benzothiophenes, wherein the following are also included:



Compound	A	Formula
261273	-(CH ₂) ₇ -	C ₃₂ H ₃₅ NO ₄ S
261274	-(CH ₂) ₆ -	C ₃₁ H ₃₃ NO ₄ S
261275	-(CH ₂) ₅ -	C ₃₀ H ₃₁ NO ₄ S
261276	-(CH ₂) ₃ -	C ₂₈ H ₂₇ NO ₄ S

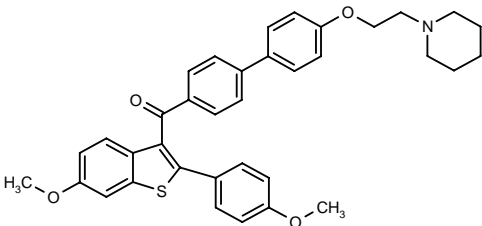
SOURCE – Lilly.

REFERENCES

1. Cullinan, G.J. and Fahey, K.J. (Eli Lilly & Co.) *Benzothiophene cpds., intermediates, processes, and methods of use*. EP 816360, JP 98067776.

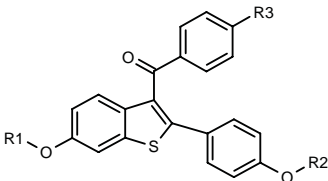
260867

1-[6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thienyl]-1-[4'-[2-(1-piperidyl)ethoxy]biphenyl-4-yl]methanone



C36-H35-N-O4-S; Mol wt: 577.74

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disease, hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis. A representative compound from a series of benzothiophene derivatives, wherein the following are also included:



Compound	R1=R2	R3	Formula
261733	H	4-(1-Pip-CH ₂ CH ₂ O)-Ph	C ₃₄ H ₃₁ NO ₄ S
261734	Me	6-(1-Pip-CH ₂ CH ₂ O)-2-Naph	C ₄₀ H ₃₇ NO ₄ S
261735	H	6-(1-Pip-CH ₂ CH ₂ O)-2-Naph	C ₃₈ H ₃₃ NO ₄ S

SOURCE – Lilly.

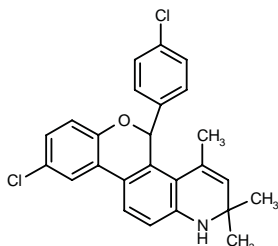
REFERENCES

1. Bryant, H.U. et al. (Eli Lilly & Co.) *Benzothiophene cpds. and methods of use*. EP 818453, JP 98067777.

LG-120794

260567

9-Chloro-5-(4-chlorophenyl)-2,2,4-trimethyl-2,5-dihydro-1H-[1]benzopyrano[3,4-f]quinoline



C25-H21-Cl2-N-O; Mol wt: 422.35

White solid.

ACTION – Nonsteroidal human progesterone receptor agonist, as demonstrated in binding ($K_i = 0.59 \pm 0.16$ nM) and cotransfection assays ($EC_{50} = 9.0 \pm 1.2$ nM; efficacy relative to progesterone [100%] = $110 \pm 9\%$). It displayed superior efficacy to medroxyprogesterone acetate in inhibiting the estradiol-induced increase in uterine wet weight in immature rats (108% vs. 100% at 1.0 mg p.o.). Potentially useful as a female contraceptive, for hormone replacement therapy and in the treatment of certain carcinomas.

SOURCE – Ligand.

REFERENCES

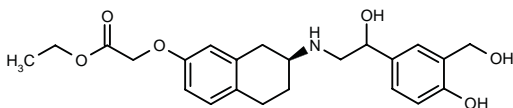
1. Jones, T.K. et al. (Ligand Pharm., Inc.) *Steroid receptor modulator cpds. and methods*. EP 800519, US 5688808, US 5688810, US 5693646, US 5693647, US 5696130, US 5696127, WO 9619458.

2. Edwards, J.P. et al. *5-Aryl-1,2-dihydro-5H-chromeno[3,4-f]quinolines as potent, orally active, nonsteroidal progesterone receptor agonists: The effect of D-ring substituents*. J Med Chem 1998, 41(3): 303.

UTERINE STIMULANTS AND TOCOLYTICS

256198

2-[7(S)-[2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethylamino]-5,6,7,8-tetrahydro-2-naphthyloxy]-acetic acid ethyl ester



C23-H29-N-O6; Mol wt: 415.49

ACTION – Selective β_2 -adrenoceptor agonist ($EC_{50} = 1.1$ nM in pregnant rat uterus) with reduced activity at β_1 -adrenoceptors ($EC_{50} = 1.1$ μ M in rat atrium), with potential for preventing preterm labor and threatened abortion, as a bronchodilator and as a lithagogue for the treatment of urinary calculus. No mortality was observed following a single dose of 30 mg/kg i.v. to mice.

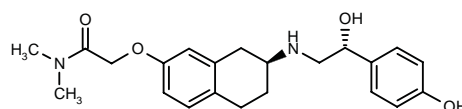
SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharm. Co., Ltd.) *3,4-Disubst. phenylethanol-aminotetralincarboxylate derivs*. WO 9735835.

257243

2-[7(S)-[2(R)-Hydroxy-2-(4-hydroxyphenyl)ethylamino]-5,6,7,8-tetrahydro-2-naphthyloxy]-N,N-dimethylacetamide



C22-H28-N2-O4; Mol wt: 384.47

ACTION – Selective β_2 -adrenoceptor agonist ($EC_{50} = 15$ nM in pregnant rat uterus) with reduced activity at β_1 -adrenoceptors ($EC_{50} = 1.6$ μ M in rat atrium), with potential for preventing preterm labor and threatened abortion, as a bronchodilator and as a lithagogue for the treatment of urinary calculus. No mortality was observed following a single dose of 50 mg/kg i.v. to mice.

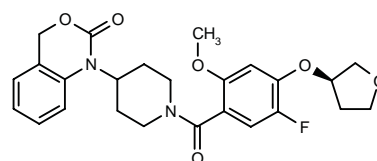
SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharm. Co., Ltd.) *Phenylethanolaminotetralincarboxamide derivs*. WO 9738970.

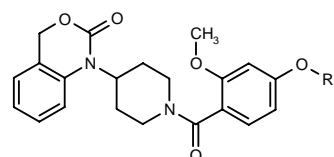
260961

1-[1-[5-Fluoro-2-methoxy-4-[tetrahydrofuran-3(R)-yl]-benzoyl]piperidin-4-yl]-2,4-dihydro-1H-3,1-benzoxazin-2-one



C25-H27-F-N2-O6; Mol wt: 470.50

ACTION – Oxytocin receptor antagonist for the treatment of preterm labor and dysmenorrhea and for stopping labor before cesarean delivery, a representative compound from a series of benzoxazinones, wherein the following are also included:



Compound	R1	Formula
261109	cis-4-NH2-cyclohexyl	C ₂₇ H ₃₃ N ₃ O ₅
261110	5-pyrimidinyl-CH(Me)	C ₂₇ H ₂₈ N ₄ O ₅
261111	exo-8-Ac-8-azabicyclo[3.2.1]oct-3-yl	C ₃₀ H ₃₅ N ₃ O ₆
261112	5-tetrazolyl-CH(Me)	C ₂₄ H ₂₆ N ₆ O ₅
261113	1-Ac-4-Pip-CH(Me)	C ₃₀ H ₃₇ N ₃ O ₆
261114	3(R)-THF	C ₂₅ H ₂₈ N ₂ O ₆

SOURCE – Merck & Co.

REFERENCES

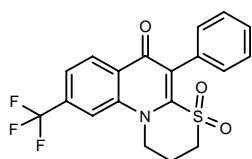
1. Sparks, M.A. et al. (Merck & Co., Inc.) *Tocolytic oxytocin receptor antagonists*. US 5726172.

DERMATOLOGIC DRUGS

TOPICAL ANTIINFLAMMATORY DRUGS

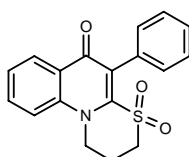
257489

5-Phenyl-9-(trifluoromethyl)-2,3-dihydro-1*H*,6*H*-[1,3]-thiazino[3,2-*a*]quinolin-6-one 4,4-dioxide



C19-H14-F3-N-O3-S; Mol wt: 393.38

ACTION – Cell adhesion inhibitor proven to inhibit the expression of E-selectin in human umbilical vein endothelial cells (HUVEC) stimulated by TNF- α (tumor necrosis factor- α), IL-1 β or LPS (lipopolysaccharide) by 104% at a concentration of 10 μ M. Mouse ear edema induced by picryl chloride was inhibited by 36% at a dose of 100 mg/kg p.o. Another representative quinolone derivative is:



260739: C18-H15-N-O3-S

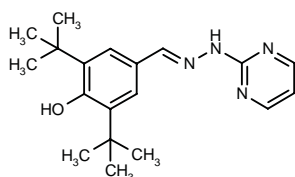
SOURCE – Kyowa Hakko.

REFERENCES

1. Tsumiki, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Quinolone derivs*. JP 97278780.

261301

3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde *N*²-(2-pyrimidin-yl)hydrazone



C19-H26-N4-O; Mol wt: 326.44

White needles, m.p. 236-7 °C.

ACTION – Antiinflammatory agent, a 5-lipoxygenase inhibitor proven to inhibit the formation of LTB₄ (IC₅₀ = 0.229 μ M in rabbit peritoneal neutrophils). It inhibited edema formation in the murine arachidonic acid-induced ear inflammation model, with 38% inhibition at 250 μ g/ear.

SOURCE – Alter.

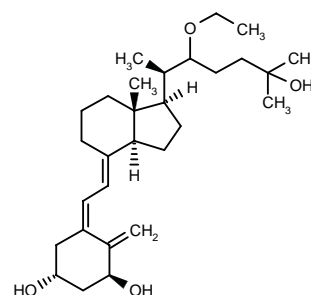
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ANTIPSORIATICS

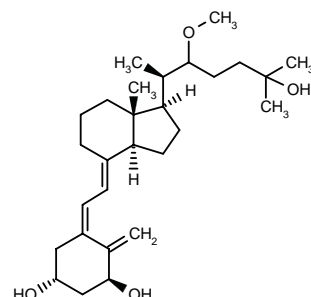
260059

(20*R*)-22-Ethoxy-1 α ,25-dihydroxyvitamin D₃



C29-H48-O4; Mol wt: 460.70

ACTION – Vitamin D analog with antiproliferative, immunosuppressive and antiinflammatory activity. Compound was found to exhibit 137-fold more potent antiproliferative properties in HaCaT cells and 161-fold more potent immunosuppressive activity in the mixed lymphocyte reaction (MLR) assay than 1 α ,25-dihydroxyvitamin D₃, while showing 2-fold lower calcemic activity. Claimed for the treatment of diseases characterized by abnormal cell differentiation and/or proliferation such as psoriasis, cancer, graft-vs.-host reaction, transplant rejection, autoimmune and inflammatory diseases, hyperparathyroidism, neurodegenerative disorders and osteoporosis. Another specifically claimed vitamin D analog is:



260709: C28-H46-O4

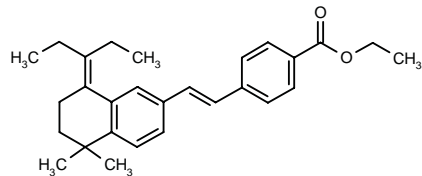
SOURCE – Leo A/S.

REFERENCES

1. Bretting, C.A.S. (Leo Pharm. Prods. Ltd. A/S) *Novel vitamin D analogues*. WO 9746522.

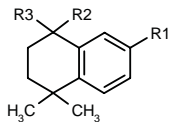
260117

4-[2-[8-(1-Ethylpropylidene)-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl]vinyl]benzoic acid ethyl ester

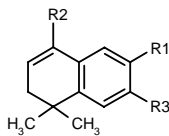


C28-H34-O2; Mol wt: 402.58

ACTION – Agent with retinoid activity and potential in the treatment of skin-related diseases such as psoriasis, acne, ichthyoses, keratoses and atopic dermatitis, as well as cancerous and precancerous conditions. Activity was evaluated by measuring inhibition of TPA-induced ornithine decarboxylase activity ($IC_{60} = 0.7 \text{ nM}$). Other compounds from this series of dihydro- and tetrahydro-naphthalene derivatives include the following:



Compound	R1	R2	R3	Formula
260910	4-(CO2Et)-PhCH=CH		-(E)-N(OEt)-	C ₂₅ H ₂₉ NO ₃
260911	4-(CO2Et)2-PhN=N		-(E)-N(OMe)-	C ₂₂ H ₂₅ N ₃ O ₃
260912	C(Me)=CHCH=CH-C(Me)=CHCO2Et		-(E)-N(OEt)-	C ₂₅ H ₃₃ NO ₃
260919	4-(CO2Et)-PhOCO		-C(Me)2-	C ₂₅ H ₂₈ O ₄
260920	4-(CO2Et)-PhNHCO		-C(Me)2-	C ₂₅ H ₂₉ NO ₃
260921	4-(CO2Et)-PhCH=CH		-SCH2CH2S-	C ₂₆ H ₃₀ O ₂ S ₂
260922	4-(CO2Et)-PhCH=CH		-O-	C ₂₃ H ₂₄ O ₃
260923	4-(CO2Et)-PhNHCO	H	2-THP-O	C ₂₇ H ₃₃ NO ₅
260924	4-(CO2Et)-PhOCO	H	2-THP-O	C ₂₇ H ₃₂ O ₆
260925	4-(CO2Et)-PhN=N	H	OCH2OMe	C ₂₃ H ₂₈ N ₂ O ₄



Compound	R1	R2	R3	Formula
260913	4-(CO2Et)-PhOCO	SO2Ph	H	C ₂₆ H ₂₆ O ₆ S
260914	4-(CO2Et)-PhCH=CH	SPh	H	C ₂₉ H ₂₈ O ₂ S
260915	C(Me)=CHCH=CH-C(Me)=CHCO2Et	OSO2CF3	H	C ₂₄ H ₂₇ F ₃ O ₅ S
260916	4-(CO2Et)-PhNHCO	t-Bu	H	C ₂₆ H ₃₁ NO ₃
260917	H	2-thienyl	4-(CO2Et)-PhCH=CHCO	C ₂₆ H ₂₂ O ₃ S
260918	C(Me)=CHCH=CH-C(Me)=CHCO2Et	2-thienyl	H	C ₂₇ H ₃₀ O ₂ S

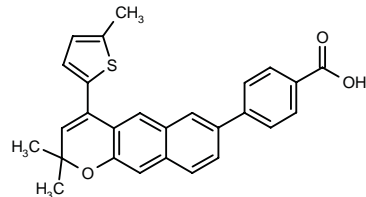
SOURCE – Allergan.

REFERENCES

1. Vuligonda, V. et al. (Allergan, Inc.) *Substd. tetrahydronaphthalene and dihydronaphthalene derivs. having retinoid and/or retinoid antagonist-like biological activity*. US 5723666, US 5741896, WO 9748672.

261293

4-[2,2-Dimethyl-4-(5-methyl-2-thienyl)-2H-naphtho[2,3-b]-pyran-7-yl]benzoic acid



C27-H22-O3-S; Mol wt: 426.53

ACTION – Agent for the treatment of skin diseases including psoriasis, keratoses, acne, ichthyoses and other keratinization and hyperproliferative disorders that exerts retinoid-like, retinoid-antagonist or retinoid inverse agonist-like biological activity and shows strong affinity for retinoid A receptors (RAR), as demonstrated in a binding assay ($K_d = 17, 12 \text{ and } 33 \text{ nM}$ for RAR α , RAR β and RAR γ , respectively).

SOURCE – Allergan.

REFERENCES

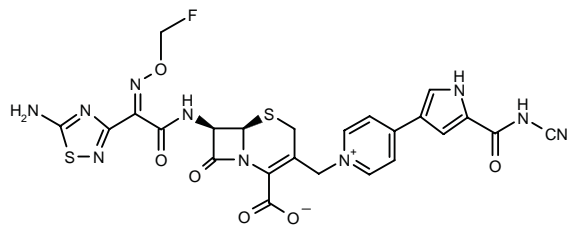
1. Vuligonda, V. et al. (Allergan) *Benzo[1,2-g]-chrom-3-ene and benzo[1,2-g]-thiochrom-3-ene derivs.* US 5728846.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

257219

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(fluoromethoxyimino)acetamido]-3-[4-[5-(*N*-cyanocarbamoyl)-1*H*-pyrrol-3-yl]pyridinium-1-ylmethyl]-3-cephem-4-carboxylate



C24-H19-F-N10-O6-S2; Mol wt: 626.60

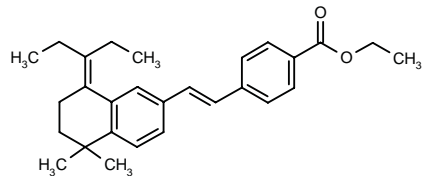
SOURCE – Leo A/S.

REFERENCES

1. Bretting, C.A.S. (Leo Pharm. Prods. Ltd. A/S) *Novel vitamin D analogues*. WO 9746522.

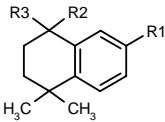
260117

4-[2-[8-(1-Ethylpropylidene)-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl]vinyl]benzoic acid ethyl ester

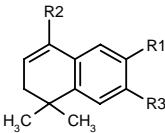


C28-H34-O2; Mol wt: 402.58

ACTION – Agent with retinoid activity and potential in the treatment of skin-related diseases such as psoriasis, acne, ichthyoses, keratoses and atopic dermatitis, as well as cancerous and precancerous conditions. Activity was evaluated by measuring inhibition of TPA-induced ornithine decarboxylase activity ($IC_{60} = 0.7 \text{ nM}$). Other compounds from this series of dihydro- and tetrahydro-naphthalene derivatives include the following:



Compound	R1	R2	R3	Formula
260910	4-(CO2Et)-PhCH=CH		-(E)-N(OEt)-	C ₂₅ H ₂₉ NO ₃
260911	4-(CO2Et)2-PhN=N		-(E)-N(OMe)-	C ₂₂ H ₂₅ N ₃ O ₃
260912	C(Me)=CHCH=CH-C(Me)=CHCO2Et		-(E)-N(OEt)-	C ₂₅ H ₃₃ NO ₃
260919	4-(CO2Et)-PhOCO		-C(Me)2-	C ₂₅ H ₂₈ O ₄
260920	4-(CO2Et)-PhNHCO		-C(Me)2-	C ₂₅ H ₂₉ NO ₃
260921	4-(CO2Et)-PhCH=CH		-SCH2CH2S-	C ₂₆ H ₃₀ O ₂ S ₂
260922	4-(CO2Et)-PhCH=CH		-O-	C ₂₃ H ₂₄ O ₃
260923	4-(CO2Et)-PhNHCO	H	2-THP-O	C ₂₇ H ₃₃ NO ₅
260924	4-(CO2Et)-PhOCO	H	2-THP-O	C ₂₇ H ₃₂ O ₆
260925	4-(CO2Et)-PhN=N	H	OCH2OMe	C ₂₃ H ₂₈ N ₂ O ₄



Compound	R1	R2	R3	Formula
260913	4-(CO2Et)-PhOCO	SO2Ph	H	C ₂₆ H ₂₆ O ₆ S
260914	4-(CO2Et)-PhCH=CH	SPh	H	C ₂₉ H ₂₈ O ₂ S
260915	C(Me)=CHCH=CH-C(Me)=CHCO2Et	OSO2CF3	H	C ₂₄ H ₂₇ F ₃ O ₅ S
260916	4-(CO2Et)-PhNHCO	t-Bu	H	C ₂₆ H ₃₁ NO ₃
260917	H	2-thienyl	4-(CO2Et)-PhCH=CHCO	C ₂₆ H ₂₂ O ₃ S
260918	C(Me)=CHCH=CH-C(Me)=CHCO2Et	2-thienyl	H	C ₂₇ H ₃₀ O ₂ S

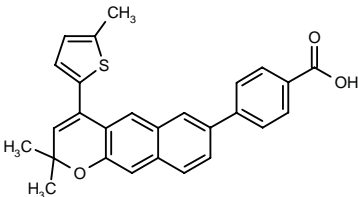
SOURCE – Allergan.

REFERENCES

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261293

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C27-H22-O3-S; Mol wt: 426.53

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SOURCE – Allergan.

REFERENCES

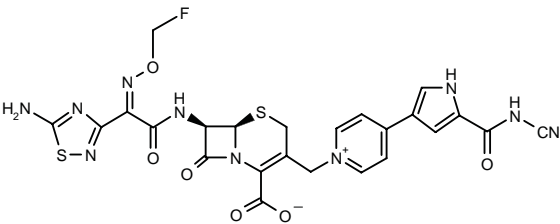
1. Vuligonda, V. et al. (Allergan) *Benzo[1,2-g]-chrom-3-ene and benzo[1,2-g]-thiochrom-3-ene derivs.* US 5728846.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

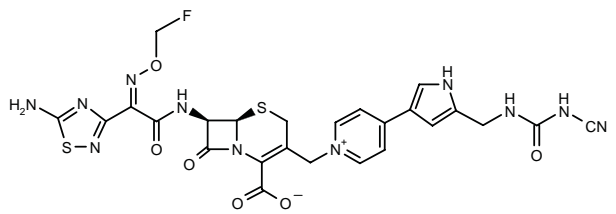
257219

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(fluoromethoxyimino)acetamido]-3-[4-[5-(*N*-cyanocarbamoyl)-1*H*-pyrrol-3-yl]pyridinium-1-ylmethyl]-3-cephem-4-carboxylate



C24-H19-F-N10-O6-S2; Mol wt: 626.60

ACTION – Cephem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus pyogenes* C-203 (MIC = 0.006 µg/ml) and *Klebsiella pneumoniae* SR1 (MIC = 0.006 µg/ml). Also active *in vivo* in mice infected with different microorganisms such as *Staphylococcus aureus* Smith, *Proteus vulgaris* GN-329 and *Pseudomonas aeruginosa* SR24. Another exemplified compound is:



260436: C25-H22-F-N11-O6-S2

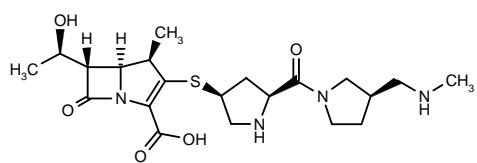
SOURCE – Shionogi.

REFERENCES

1. Nishitani, Y. and Ishikura, K. (Shionogi & Co., Ltd.) *Cephem cpds. and drugs containing the cpds.* WO 9737996.

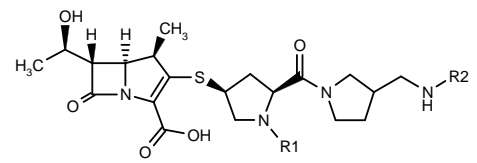
257766

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[2(*S*)-[3(*R*)-(methylaminomethyl)pyrrolidin-1-ylcarbonyl]pyrrolidin-4(*S*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



C21-H32-N4-O5-S; Mol wt: 452.57

ACTION – Carbapenem antibiotic with potent *in vitro* activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P (MIC < 0.01-0.02 µg/ml), *Escherichia coli* NIHJ (MIC < 0.01-0.02 µg/ml) and *Pseudomonas aeruginosa* No. 7 and 3719 (MIC = 0.05-0.2 µg/ml). It was also active *in vivo* in protecting against mortality in mice infected with *P. aeruginosa* 1008 (ED₅₀ = 0.22 mg/kg s.c.), with efficacy comparable or superior to meropenem (ED₅₀ = 0.72 mg/kg s.c.). A compound within a series of 1-methylcarbapenem derivatives, wherein the following are also included:



Compound	R1	R2	Isomer	Formula
262203	Me	Me	R	C ₂₂ H ₃₄ N ₄ O ₅ S
262204	H	Me	S	C ₂₁ H ₃₂ N ₄ O ₅ S
262205	Me	Me	S	C ₂₂ H ₃₄ N ₄ O ₅ S
262206	Me	H	R	C ₂₁ H ₃₂ N ₄ O ₅ S
262207	Me	H	S	C ₂₁ H ₃₂ N ₄ O ₅ S
262208	H	C(=NH)NH2	R	C ₂₁ H ₃₂ N ₆ O ₅ S

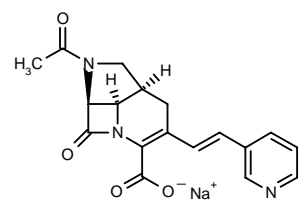
SOURCE – Sankyo.

REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *1-Methylcarbapenem derivs.* JP 98036370, WO 9741123.

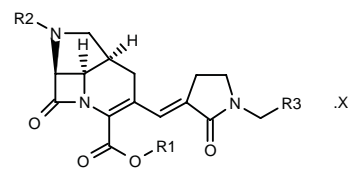
259866

(1*aS*,3*aR*,6*bR*)-2-Acetyl-1-oxo-5-[2(*E*)-(3-pyridyl)vinyl]-1*a*,2,3,3*a*,4,6*b*-hexahydro-1*H*-2,6*a*-diazacyclobut[*cd*]-indene-6-carboxylic acid sodium salt

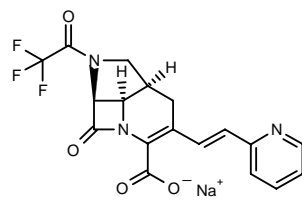


C18-H16-N3-Na-O4; Mol wt: 361.33

ACTION – β-Lactamase inhibitor and antibacterial agent giving an IC₅₀ of 0.010 µM against β-lactamase from *Citrobacter freundii* 1982 and MIC values of 8 and 2 µg/ml against *C. freundii* 1982 and *Staphylococcus aureus* 887, respectively. Within this series of β-lactams, the following are also included:



Compound	R1	R2	R3	X	Formula
260654	H	H	4-NO2-Ph	CF3CO2H	C ₂₁ H ₂₀ N ₄ O ₆ .C ₂ HF ₃ O ₂
260655	Na ⁺	4-(CONH2)-PhNHCO	CF3		C ₂₄ H ₂₁ F ₃ N ₅ NaO ₆
260656	Na ⁺	COCF3	2-thienyl		C ₂₁ H ₁₇ F ₃ N ₃ NaO ₅ S



260657: C18-H13-F3-N3-Na-O4

SOURCE – Roche.

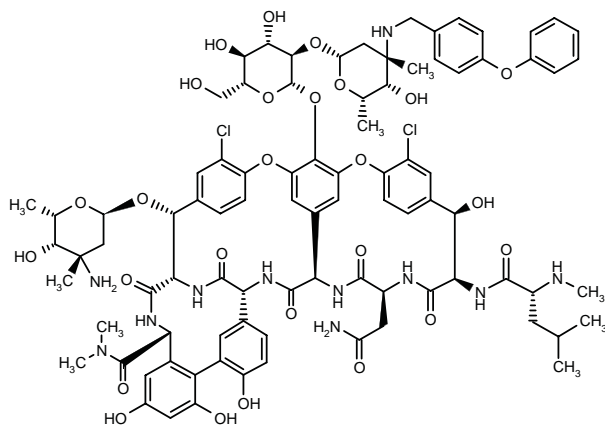
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1. Böhringer, M. and Pflieger, P. (F. Hoffmann-La Roche AG) *β-Lactams.* WO 9745429.

MISCELLANEOUS ANTIBIOTICS

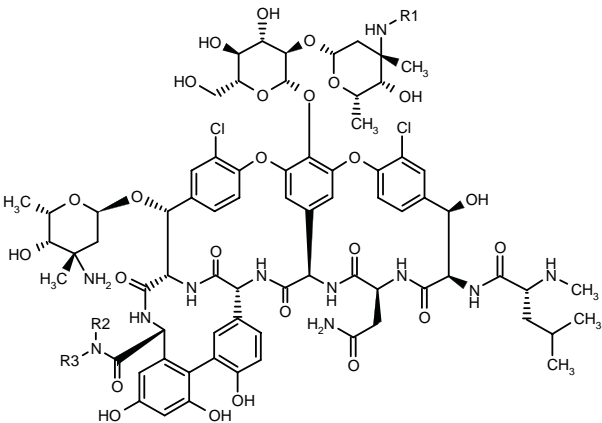
260856

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl- α -L-galactopyranosyloxy)-3-(carbamoylmethyl)-10,19-dichloro-7,28,30,32-tetrahydroxy-*N,N*-dimethyl-6-(*N* ^{α} -methyl-D-leucylamino)-2,5,24,38,39-pentaoso-44-[2-*O*-[2,3,6-trideoxy-3-*C*-methyl-3-(4-phenoxybenzylamino)- β -L-galactopyranosyl]- β -D-glucopyranosyloxy]-2,3,4,5,6,7,23,24,25,26,36,37,38,38*a*-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,26-(iminomethano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclopentacosine-26-carboxamide



C88-H103-Cl2-N11-O26; Mol wt: 1801.75

ACTION – Glycopeptide antibiotic derived from A-82846B (chloroorienticin A) and reported to be particularly useful against Gram-positive bacteria including vancomycin-resistant enterococci (VRE). For example, it gave MIC values against *Staphylococcus aureus* 447, *Streptococcus haemolyticus* 415, *Staphylococcus epidermidis* 270, *Streptococcus pneumoniae* P1 and *Streptococcus pyogenes* 203 of 1, 2, 0.25, 0.125 and 0.06 μ g/ml, respectively. Other related glycopeptides include the following:



Compound	R1	R2=R3	Formula
261406	4-Ph-PhCH2	Me	C ₈₈ H ₁₀₃ Cl ₂ N ₁₁ O ₂₅
261407	4-Ph-PhCH2	Bu	C ₉₄ H ₁₁₅ Cl ₂ N ₁₁ O ₂₅
261408	4-Ph-PhCH2	t-Bu	C ₉₄ H ₁₁₅ Cl ₂ N ₁₁ O ₂₅
261409	4-Ph-O-PhCH2	CH2Ph	C ₁₀₀ H ₁₁₁ Cl ₂ N ₁₁ O ₂₆
261410	4-Ph-PhCH2	CH2Ph	C ₁₀₀ H ₁₁₁ Cl ₂ N ₁₁ O ₂₅
261411	H	CH2CH2Ph	C ₈₉ H ₁₀₅ Cl ₂ N ₁₁ O ₂₅
261412	H	(CH2)3Ph	C ₉₁ H ₁₀₉ Cl ₂ N ₁₁ O ₂₅

SOURCE – Lilly.

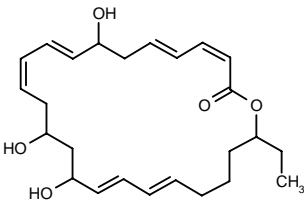
REFERENCES

1. Cooper, R.D.G. et al. (Eli Lilly & Co.) *Glycopeptide antibiotic amide derivs.* EP 816378, WO 9800153.

MACROLACTINE M

258445

7,13,15-Trihydroxy-2(*Z*),4(*E*),8(*E*),10(*Z*),16(*E*),18(*E*)-pentacosahexaeno-23-lactone



C25-H36-O5; Mol wt: 416.56

ACTION – Macrolide antibacterial agent isolated from *Bacillus* sp. PP19-H3 (FERM P-15407).

SOURCE – Ocean Biotechnology.

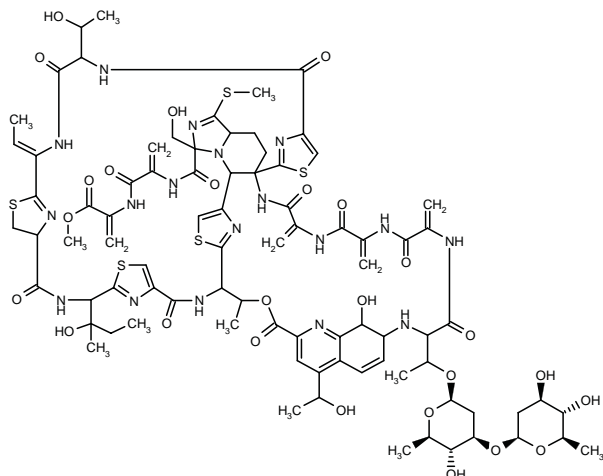
REFERENCES

1. Nagao, T. et al. (Ocean Biotechnology) *Novel macrolactone and preparation method thereof.* JP 97301970.

SCH-40832

260755

2-[2-[48-[1-[2,6-Dideoxy-3-*O*-(2,6-dideoxy-β-D-glucopyranosyl)-β-D-glucopyranosyloxy]ethyl]-15-ethylidene-41-hydroxy-12,45-bis(1-hydroxyethyl)-1-(hydroxymethyl)-22-(1-hydroxy-1-methylpropyl)-36-methyl-51,57-bis(methylene)-3-(methylsulfanyl)-10,13,20,27,38,49,52,55,58-nonaoxo-1,3a,4,5,10,11,12,13,14,15,19,20,21,22,28,29,33a,36,41,42-icosahydro-18*H*,27*H*-5a,29-(iminoethaniminoethaniminoethaniminoethanimino[7,2]quinolinomethanoxymethano)-9,6:19,16:26,23:33,30-tetranitriloimidazo[1',5':1,6]-pyrido[3,2-*m*][1,11,17,24,4,7,20,27]tetrathiatetraazacyclotriacontin-1-ylcarboxamido]-2-propenamido]-2-propenoic acid methyl ester



C84-H104-N18-O26-S5; Mol wt: 1942.15

ACTION – Disaccharide-containing, sulfur-rich peptide antibiotic isolated as a minor component of the antibiotic complex produced by *Micromonospora carbonacea* var. *africana* (ATCC 39149). It was active *in vitro* against Gram-positive bacteria in the range of 0.1-1.0 µg/ml.

SOURCE – Schering-Plough.

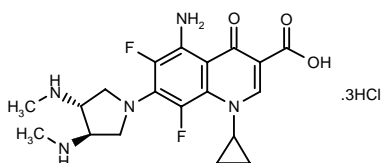
REFERENCES

1. Puar, M.S. et al. *Sch 40832: A novel thioestrept from Micromonospora carbonacea*. *J Antibiot* 1998, 51(2): 221.

MISCELLANEOUS ANTIBACTERIAL DRUGS

261133

(3*R*,4*R*)-5-Amino-1-cyclopropyl-7-[3,4-di(methylamino)pyrrolidin-1-yl]-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid trihydrochloride



C19-H23-F2-N5-O3.3HCl; Mol wt: 516.80

ACTION – Potent quinolone antibiotic proven effective *in vitro* against both Gram-negative and Gram-positive bacteria. It showed activity against Gram-positive bacteria comparable to norfloxacin and ciprofloxacin, giving MIC values of 0.25 µg/ml against methicillin-resistant *Staphylococcus aureus*, as well as against *Staphylococcus epidermidis* (MIC = 1.0 µg/ml), *Streptococcus faecalis* (MIC = 0.25-1.0 µg/ml) and *Streptococcus pyogenes* (MIC = 0.03 µg/ml). It also showed activity against some Gram-negative bacteria such as sensitive *Escherichia coli* (MIC = 0.06-0.5 µg/ml), *Pseudomonas aeruginosa* (MIC = 0.25-1.0 µg/ml) and *Salmonella typhi* (MIC = 0.125 µg/ml), although it did not exhibit any significant activity against ciprofloxacin-resistant strains (MIC > 8.0 µg/ml).

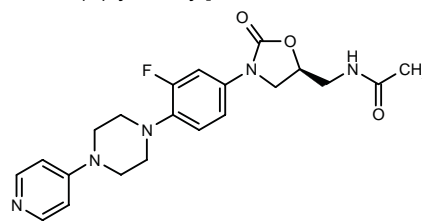
SOURCE – Dr. Reddy's Res. Found., Hyderabad (IN).

REFERENCES

1. Lohray, B.B. et al. *Novel quinolone derivatives as potent antibacterials*. *Bioorg Med Chem Lett* 1998, 8(5): 525.

261208

N-[3-[3-Fluoro-4-[4-(4-pyridyl)piperazin-1-yl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C21-H24-F-N5-O3; Mol wt: 413.45

ACTION – Oxazolidinone antibacterial agent with *in vitro* activity against Gram-positive organisms such as *Staphylococcus aureus* Oxford (MIC = 1.0 µg/ml), methicillin/quinolone-resistant *S. aureus* (MIC = 8.0 µg/ml), methicillin-resistant coagulase-negative staphylococci (MIC = 2.0 µg/ml), *Streptococcus pyogenes* C203 (MIC = 2.0 µg/ml), *Enterococcus faecalis* (MIC = 2.0 µg/ml) and *Bacillus subtilis* (MIC = 1.0 µg/ml).

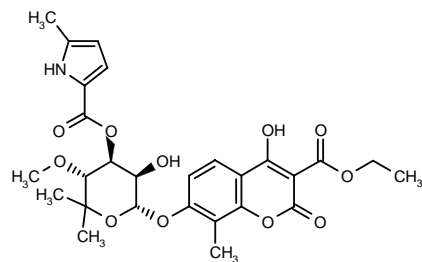
SOURCE – Zeneca.

REFERENCES

1. Betts, M.J. and Darbyshire, C.J. (Zeneca, Ltd.) *Pyridyl-piperazinyl-phenyl-oxazolidinone derivs. and their use as antibacterials*. WO 9801447.

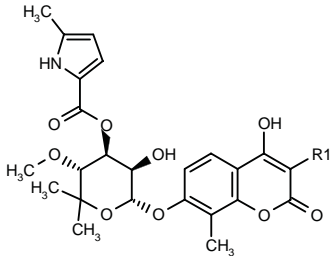
260112

7-[6-Deoxy-5-methyl-4-*O*-methyl-3-*O*-(5-methyl-1*H*-pyrrol-2-ylcarbonyl)-α-L-mannopyranosyloxy]-4-hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-3-carboxylic acid ethyl ester



C27-H31-N-O11; Mol wt: 545.54

ACTION – Antibacterial agent that inhibits DNA supercoiling (DNA gyrase) and is reportedly active against Gram-positive bacteria, particularly staphylococci, with MIC values of 0.04-20 µg/ml. Other specifically claimed ribose-substituted aromatic derivatives include the following:



Compound	R1	Formula
260790	Ac	C ₂₆ H ₂₉ NO ₁₀
260791	C(Me)=NOMe	C ₂₇ H ₃₂ N ₂ O ₁₀
261685	COCH ₂ OEt	C ₂₈ H ₃₃ NO ₁₁
261686	cyclopropyl-CO	C ₂₈ H ₃₁ NO ₁₀
261687	CONH ₂	C ₂₈ H ₂₈ N ₂ O ₁₀

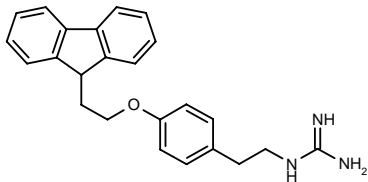
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Klich, M. et al. (Roussel Uclaf) *Novel aromatic derivs. substd. by a ribose, their method of preparation and application as medicine.* WO 9747634.

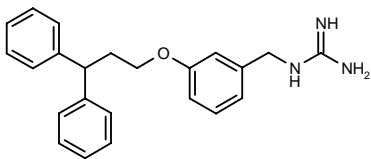
260118

N-[2-[4-[2-(9*H*-Fluoren-9-yl)ethoxy]phenyl]ethyl]guanidine

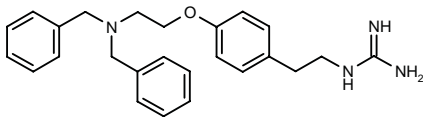


C24-H25-N3-O; Mol wt: 371.48

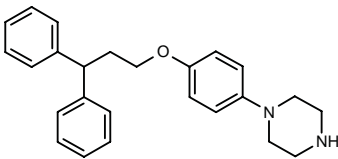
ACTION – Antibacterial agent that acts by inhibiting the autophosphorylation of bacterial histidine kinases and the transfer of phosphate from phosphorylated histidine kinases to the phosphate acceptor proteins involved in the regulation of bacterial gene expression. *In vitro*, compound inhibited the autophosphorylation of kinase A with an IC₅₀ value of 19.8 µM. Other specifically claimed diaryl compounds include the following:



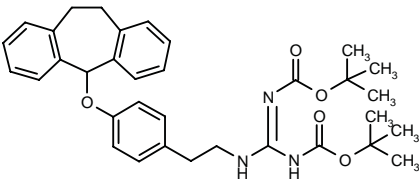
261026: C23-H25-N3-O



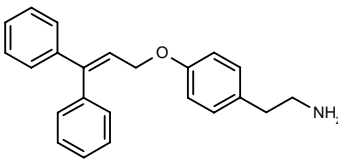
261027: C25-H30-N4-O



261028: C25-H28-N2-O



261029: C34-H41-N3-O5



262197: C23-H23-NO

SOURCE – Ortho.

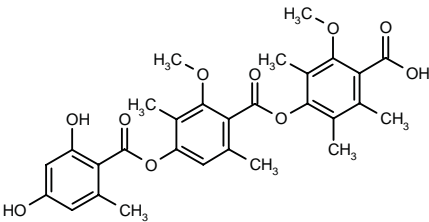
REFERENCES

1. Kanojia, R.M. et al. (Ortho Pharm. Corp.) *Diaryl antimicrobial agents.* WO 9748674.

15352A

261138

4-[4-(2,4-Dihydroxy-6-methylbenzoyloxy)-2-methoxy-3,6-dimethylbenzoyloxy]-2-methoxy-3,5,6-trimethylbenzoic acid



C29-H30-O10; Mol wt: 538.55

ACTION – Antibacterial agent structurally related to thielavin B isolated from a culture of the fungus *Thielavia terricola* AA15352; it acts by inhibiting bacterial cell wall synthesis. Compound is expected to act synergistically with vancomycin.

SOURCE – Millennium.

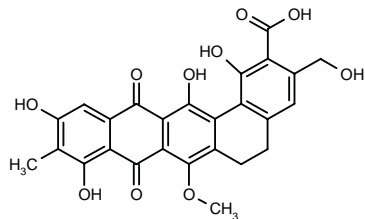
REFERENCES

1. Rothstein, D. et al. (Millennium Pharm., Inc.) *Novel antibacterial cpds.* WO 9800019.

BE-39589B-1

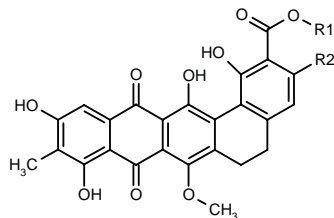
260535

1,9,11,14-Tetrahydroxy-3-(hydroxymethyl)-7-methoxy-10-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenzo[*a*]-naphthacene-2-carboxylic acid



C26-H20-O10; Mol wt: 492.44

ACTION – Antibacterial agent isolated from *Microtetraspora* sp. A39589 (FERM P-15369), active against Gram-positive bacteria including *Bacillus subtilis* ATCC 6633 (MIC = 1.56 µg/ml), *Bacillus cereus* IFO 3001 (MIC = 0.78 µg/ml), *Staphylococcus aureus* FDA 209P (MIC = 1.56 µg/ml) and methicillin-resistant *S. aureus* 6117 and 6118 (MIC = 1.56 and 1.56 µg/ml, respectively). Other compounds obtained from the same source are:



Compound	R1	R2	Formula
BE-39589B-2 [261422]	-CH2-		C ₂₆ H ₁₈ O ₉
BE-39589C-2 [261423]	H	CO ₂ Me	C ₂₇ H ₂₀ O ₁₁

SOURCE – Banyu.

REFERENCES

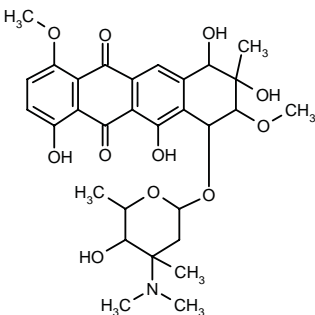
1. Tsukamoto, M. et al. (Banyu Pharm. Co., Ltd.) *Antibacterial substances BE-39589 and their preparation method*. JP 98017527.

ANTIMYCOBACTERIAL AGENTS

NOTHRAMICIN

260750

10-[4-(Dimethylamino)-5-hydroxy-4,6-dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy]-1,7,8,11-tetrahydroxy-4,9-dimethoxy-8-methyl-7,8,9,10-tetrahydronaphthacene-5,12-dione



C30-H37-N-O11; Mol wt: 587.62

Red powder, m.p. 140-5 °C.

ACTION – Anthracycline antibiotic isolated from the culture broth of *Nocardia* sp. MJ896-43F17, proven to inhibit the growth of mycobacteria such as *Mycobacterium smegmatis* ATCC 607 (MIC = 1.56 µg/ml), a range of resistant *M. smegmatis* ATCC 607 strains (MIC = 6.25 µg/ml), *Mycobacterium phlei* (MIC = 6.25 µg/ml), *Mycobacterium vaccae* ATCC 15483 (MIC = 12.5 µg/ml) and *Mycobacterium fortuitum* (MIC = 25.0 µg/ml); however, it exhibited no effect against Gram-positive or Gram-negative bacteria and yeasts. Nothramicin exhibited low acute toxicity in mice (LD₅₀ > 100 mg/kg i.v.).

SOURCE – Inst. Microbial Chem., Tokyo (JP).

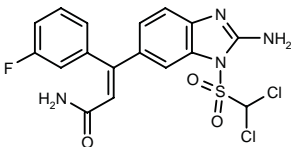
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ANTIVIRAL DRUGS

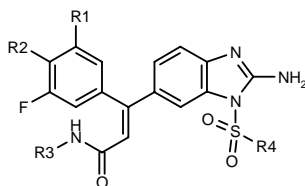
259916

3-[2-Amino-1-(dichloromethylsulfonyl)benzimidazol-6-yl]-3-(3-fluorophenyl)-2(*Z*)-propenamide



C17-H13-Cl2-F-N4-O3-S; Mol wt: 443.28

ACTION – Antiviral agent for the treatment of infections caused by picornaviruses such as rhinoviruses, polioviruses, coxsackieviruses and echoviruses, and flaviviruses such as hepatitis C virus (HCV). Compound is believed to inhibit viral replication by interfering with the structure and/or function of the viral replication complex, and is suggested to inhibit the function of viral gene 3A in rhinoviruses and enteroviruses and the NS2 or NS4 protein in HCV. Other specifically claimed compounds from this series of benzimidazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
260658	H	H	H	Pr	C ₁₉ H ₁₉ FN ₄ O ₃ S
260659	H	H	Me	1-pyrrolidinyl	C ₂₁ H ₂₂ FN ₄ O ₃ S
260660	H	H	H	2-thienyl	C ₂₀ H ₁₅ FN ₄ O ₃ S ₂
260661	H	F	Me	i-Pr	C ₂₀ H ₂₀ F ₂ N ₄ O ₃ S
260662	H	F	H	i-Pr	C ₁₉ H ₁₈ F ₂ N ₄ O ₃ S
260663	H	OMe	Me	i-Pr	C ₂₁ H ₂₃ FN ₄ O ₄ S
260664	H	OMe	H	i-Pr	C ₂₀ H ₂₁ FN ₄ O ₄ S
260665	F	H	Me	i-Pr	C ₂₀ H ₂₀ F ₂ N ₄ O ₃ S
260666	F	H	H	i-Pr	C ₁₉ H ₁₈ F ₂ N ₄ O ₃ S

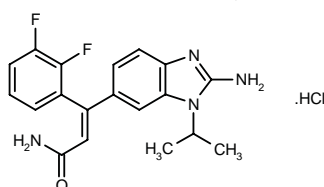
SOURCE – Lilly.

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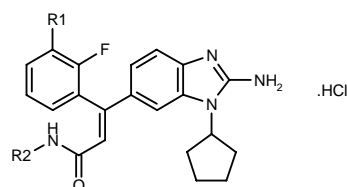
259917

3-(2-Amino-1-isopropylbenzimidazol-6-yl)-3-(2,3-difluorophenyl)-2(Z)-propenamide hydrochloride



C₁₉-H₁₈-F₂-N₄-O.HCl; Mol wt: 392.84

ACTION – Antiviral agent active against picornaviruses such as rhinoviruses, polioviruses, coxsackieviruses and echoviruses, and flaviviruses such as hepatitis C virus (HCV); it appears to inhibit viral replication by interfering with the structure and/or function of the viral replication complex, and may inhibit the 3A viral gene product in rhinoviruses and enteroviruses and the analogous NS2 or NS4 protein in HCV. A representative compound from a series of specifically claimed benzimidazole derivatives, wherein the following are also included:



Compound	R1	R2	Formula
260675	F	H	C ₂₁ H ₂₀ F ₂ N ₄ O.HCl
260676	H	H	C ₂₁ H ₂₁ FN ₄ O.HCl
260677	H	Me	C ₂₂ H ₂₃ FN ₄ O.HCl

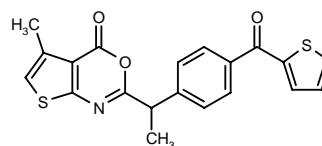
SOURCE – Lilly.

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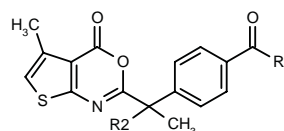
260138

5-Methyl-2-[1-[4-(2-thienylcarbonyl)phenyl]ethyl]-4H-thieno[2,3-d][1,3]oxazin-4-one



C₂₀-H₁₅-N-O₃-S₂; Mol wt: 381.46

ACTION – Antiviral agent, an inhibitor of herpesvirus protease (IC₅₀ = 0.5 μM or less against cytomegalovirus protease) useful in the treatment of infections caused by herpesviruses, particularly cytomegalovirus and herpes simplex type 2 (HSV-2). Within this series of 4H-3,1-benzoxazin-4-one derivatives, the following are also included:



Compound	R1	R2	Formula
260973	2-thienyl	Cl	C ₂₀ H ₁₄ ClNO ₃ S ₂
260974	2-furyl	H	C ₂₀ H ₁₅ NO ₄ S
260975	3-Pyr	H	C ₂₁ H ₁₆ N ₂ O ₃ S

SOURCE – SmithKline Beecham.

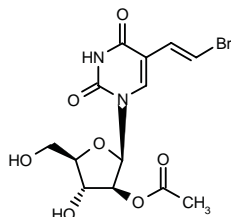
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1. McNair, D.J. et al. (SmithKline Beecham plc) *4H-3,1-Benzoxazin-4-one derivs. and analogs as antiviral agents.* WO 9748707.

260821

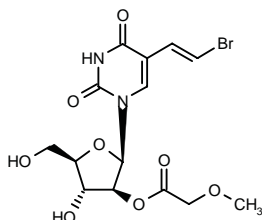
(*E*)-1-(2-*O*-Acetyl-β-D-arabinofuranosyl)-5-(2-bromovinyl)-2,4(1*H*,3*H*)-pyrimidinedione

(*E*)-1-(2-*O*-Acetyl-β-D-arabinofuranosyl)-5-(2-bromovinyl)-uracil



C13-H15-Br-N2-O7; Mol wt: 391.17

ACTION – Antiviral agent, a sorivudine prodrug with potent activity against varicella-zoster virus (VZV) *in vitro* (EC_{50} = 7.1 ng/ml in human embryo lung fibroblast cells). It shows an improved pharmacokinetic profile due to its greater aqueous solubility and enzymatic stability. Another sorivudine prodrug with similar characteristics is:



260822: C14-H17-Br-N2-O8

These prodrugs undergo liver esterase-catalyzed hydrolysis to the parent compound. The retarded rates of hydrolysis suggest that they may act as lipophilic prodrugs providing increased plasma and cellular concentrations.

SOURCE – Yamasa Shoyu.

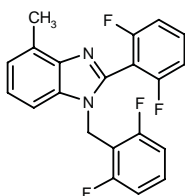
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1. Baraldi, P.G. et al. *Facile access to 2'-O-acyl prodrugs of 1-(beta-D-arabinofuranosyl)-5(E)-(2-bromovinyl)uracil (BVArAU) via regioselective esterase-catalyzed hydrolysis of 2',3',5'-triesters*. Tetrahedron Lett 1993, 34(19): 3177.
2. Manfredini, S. et al. *Enzymatic synthesis of 2'-O-acyl prodrugs of 1-(beta-D-arabinofuranosyl)-5(E)-(2-bromovinyl)uracil and of 2'-O-acyl-araU, -araC and -araA*. Antivir Chem Chemother 1998, 9(1): 25.

AIDS MEDICINES

259164

1-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)-4-methyl-1*H*-benzimidazole



C21-H14-F4-N2; Mol wt: 370.35

ACTION – Non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI), the best compound from a series of 2-aryl-substituted benzimidazoles, giving an IC_{50} value of 0.20 μ M for inhibition of wild-type HIV-1 reverse transcriptase and an EC_{50} value of 0.44 μ M against HIV-1 in CEM-SS cells; it retained activity against resistant HIV-1 strains, including strains resistant to NNRTIs, and showed low cytotoxicity.

SOURCES – Natl. Cancer Inst.-Frederick Cancer Res. Develop. Center, Frederick, MD (US); Southern Res. Inst.-Frederick Res. Center, Frederick, MD (US).

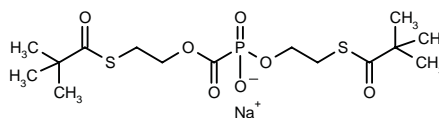
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260820

(Hydroxy)[2-(pivaloylsulfanyl)ethoxy]phosphorylcarboxylic acid 2-(pivaloylsulfanyl)ethyl ester sodium salt

[2-(*S*-Pivaloylsulfanyl)ethoxycarbonyl]phosphonic acid 2-(*S*-pivaloylsulfanyl)ethyl monoester sodium salt



C15-H26-Na-O7-P-S2; Mol wt: 436.45

Colorless, fluffy, hygroscopic compound, m.p. > 220 °C.

ACTION – Antiviral agent for AIDS, a foscarnet prodrug proven active *in vitro* against both HIV-1_{IIIB} (EC_{50} = 44 \pm 14 μ M in MT-4 cells) and HIV-1_{LAI} (EC_{50} = 27 \pm 10 and 20 \pm 3 μ M, respectively, in CEM-SS and thymidine kinase-deficient CEM-TK⁻ cells), with relatively low cytotoxicity (CC_{50} > 100 μ M in all cell lines); it was more effective than the parent compound. Title compound did not show any activity against hepatitis B virus (HBV) in 2.2.15 cells.

SOURCES – Univ. Alabama, Birmingham, AL (US); Astra Arcus; INSERM; Julius-Maximilians-Univ., Würzburg (DE); Univ. Manchester, Manchester (GB); Univ. Montpellier, Montpellier (FR).

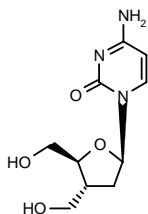
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BEA-005*

166533

1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)- β -D-*erythro*-pentofuranosyl]cytosine



C10-H15-N3-O4; Mol wt: 241.25

Hydrochloride salt, m.p. 153-7 °C, $[\alpha]_D^{20} +11.5^\circ$ (c 1.01, MeOH).

ACTION – Antiviral agent for AIDS, a nucleoside analog with *in vitro* activity against HIV, SIV, various herpesviruses and hepatitis B virus. It was able to prevent acute SIV and HIV-2 infection in cynomolgus monkeys when treatment was initiated either before or after virus inoculation.

SOURCES – Bristol-Myers Squibb; Lilly; Medivir.

REFERENCES

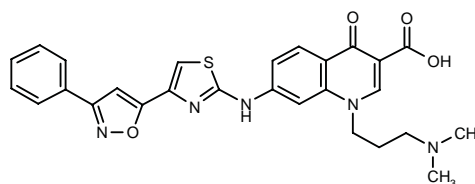
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- Borg, N. et al. *Pharmacokinetics of 2,3-dideoxy-3-hydroxymethylcytidine (BEA005) in monkeys and rats*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst I-83.
- Böttiger, D. et al. *Prevention of SIV and HIV-2 infections in monkeys by pre- and postexposure treatment with BEA005*. 1st Eur Conf Exp AIDS Res (March 10-13, Cannes) 1996, Abst 183-S6.
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- Faul, M.M. et al. *Synthesis of 2',3'-dideoxy-3'-hydroxymethylcytidine; a unique antiviral nucleoside*. Tetrahedron 1997, 53(24): 8085.
- Mann, J. et al. *Photocatalyzed addition of alcohols to 5-substituted 2,5-dihydrofuran-2-ones: Novel synthesis of (3'R)-2',3'-dideoxy-3'-hydroxymethyl nucleosides*. J Chem Soc Perkin Trans I 1994, 21: 3141.
- Mann, J. and Weymouth-Wilson, A. *The stereoselective photochemical addition of alcohols to 5-substituted furan-2(5H)-ones*. Synlett 1992, 67.
- Sanghvi, Y.S. et al. *Large-scale synthesis of 3'-deoxy-3'-C-formyl thymidine: An efficient entry into 3'-branched nucleosides*. 207th ACS Natl Meet (March 13-17, San Diego) 1994, Abst CARB 76.

*Identified compound **166533** Drug Data Rep 1991, 13(2): 159.

PD-176931

260500

1-[3-(*N,N*-Dimethylamino)propyl]-4-oxo-7-[4-(3-phenylisoxazol-5-yl)thiazol-2-ylamino]-1,4-dihydroquinoline-3-carboxylic acid



C27-H25-N5-O4-S; Mol wt: 515.59

ACTION – Potent HIV-1 integrase inhibitor, a substituted quinolone that binds to the core domain and inhibits both HIV-1 integrase processing and disintegration reactions, giving an IC₅₀ of 297 nM in the integrase processing assay.

SOURCE – Warner-Lambert.

REFERENCES

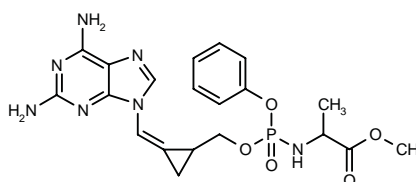
- Gogliotti, R.D. et al. *Quinolones as novel HIV integrase inhibitors*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 641.

QYL-685

260498

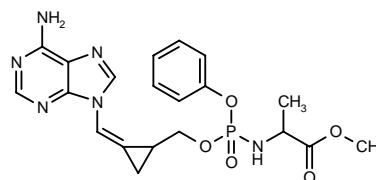
2-[*N*-[[2-[(*Z*)-(2,6-Diamino-9*H*-purin-9-yl)methylene]-cyclopropylmethoxy](phenoxy)phosphoryl]amino]propionic acid methyl ester

(*Z*)-*N*-[2-(2,6-Diaminopurin-9-ylmethylene)-cyclopropylmethoxy(phenoxy)phosphoryl]-D,L-alanine methyl ester



C20-H24-N7-O5-P; Mol wt: 473.43

ACTION – Anti-HIV agent with highly potent and specific antiviral activity against wild-type HIV-1 and HIV-2 strains and HIV-1 clones resistant to zidovudine, didanosine and multiple nucleoside reverse transcriptase inhibitors; an M184I mutation was found to be responsible for resistance to the compound. Another cyclopropane analog with a similar antiviral and resistance profile is:



QYL-609 [260328]: C20-H23-N6-O5-P

SOURCES – Natl. Inst. Health, Bethesda, MD (US); Wayne State Univ., Detroit, MI (US).

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1. Yoshimura, K. et al. *In vitro anti-HIV-1 activity and viral drug resistance profiles against phosphoralaninate diesters of Z- and E-methylenecyclopropane analogues*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 627.

T-134

261304

L-Arginyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-D-lysyl-L-prolyl-L-tyrosyl-L-arginyl-L-citrullinyl-L-cysteinyl-L-arginine

C88-H142-N34-O19-S2; Mol wt: 2044.43

ACTION – Tachyplesin peptide analog with potent anti-HIV activity, inhibiting HIV-1-induced cytopathogenicity in MT-4 cells with an EC_{50} of 3.7 nM and HIV-1 antigen expression with an IC_{50} of 14 nM, while showing low cytotoxicity (CC_{50} = 120 μ M), giving a selectivity index value (CC_{50}/EC_{50}) of 33,000. Other related tachyplesin peptide derivatives include the following:

L-Arginyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-L-lysyl-L-glycyl-L-tyrosyl-L-arginyl-L-lysyl-L-cysteinyl-L-arginine

T-121 [261305]: C85-H139-N33-O17

L-Arginyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-L-lysyl-L-glycyl-L-tyrosyl-L-arginyl-L-lysyl-L-cysteinyl-L-glutamic acid

T-122 [261306]: C84-H134-N30-O19-S2

L-Arginyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-L-lysyl-L-glycyl-L-glutamyl-L-arginyl-L-lysyl-L-cysteinyl-L-arginine

T-125 [261307]: C81-H137-N33-O18-S2

L-Arginyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-glutamyl-L-lysyl-L-lysyl-L-glycyl-L-tyrosyl-L-arginyl-L-lysyl-L-cysteinyl-L-arginine

T-128 [261308]: C84-H134-N30-O19-S2

L-Arginyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-D-lysyl-L-prolyl-L-tyrosyl-L-arginyl-L-lysyl-L-cysteinyl-L-arginine

T-132 [261309]: C88-H143-N33-O17-S2

L-Citrullinyl-L-arginyl-L-tryptophyl-L-cysteinyl-L-tyrosyl-L-arginyl-L-lysyl-D-lysyl-L-prolyl-L-tyrosyl-L-arginyl-L-lysyl-L-cysteinyl-L-arginine

T-138 [261310]: C88-H142-N32-O19-S2

SOURCE – Seikagaku.

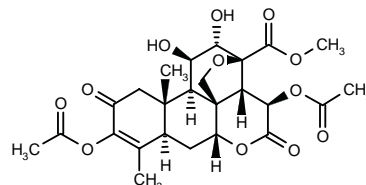
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TREATMENT OF PROTOZOAL DISEASES

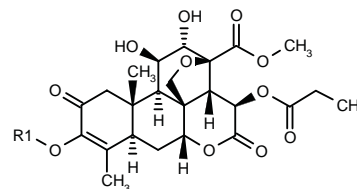
261118

[1*R*-(1 α ,2 β ,3 α ,3 α ,4 α ,6 α ,7 α β ,11 α ,11 β β ,11 α)]-4,9-Diacetyloxy-1,2-dihydroxy-8,11a-dimethyl-5,10-dioxo-2,3,3a,4,5,6a,7,7a,10,11,11a,11b-dodecahydro-1*H*-3,11c-(epoxymethano)phenanthro[10,1-*bc*]pyran-3-carboxylic acid methyl ester



C25-H30-O12; Mol wt: 522.50

ACTION – Antimalarial agent shown to potently inhibit the growth of *Plasmodium falciparum* (EC_{50} = 39 nM), with relatively low cytotoxicity against cells of host animals (EC_{50} = 16 μ M using FM3A cells derived from a mammary tumor in mice; selectivity index of 410). Other related *O*-acylated bruceolide derivatives include the following:



Compound	R1	Formula
261117	COEt	C ₂₇ H ₃₄ O ₁₂
261119	H	C ₂₄ H ₃₀ O ₁₁

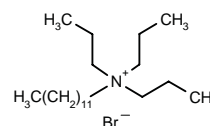
SOURCE – Okayama Univ., Okayama (JP); Osaka Univ., Osaka (JP).

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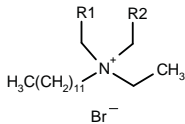
261295

N-Docecyl-N,N-tripropylammonium bromide

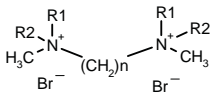


C21-H46-Br-N; Mol wt: 392.51

ACTION – Antimalarial agent, an analog of the phospholipid polar heads choline and ethanolamine with an IC_{50} for inhibition of *Plasmodium falciparum* (chloroquine-sensitive Nigerian strain) growth *in vitro* of 0.033 μ mol/l. Other related compounds include the following:



Compound	R1	R2	Formula
261296	Me	Me	C ₁₈ H ₄₀ BrN
261297	H	H	C ₁₆ H ₃₆ BrN
261298	CH ₂ OH	Me	C ₁₈ H ₄₀ BrNO



Compound	R1	R2	n	Formula
261299	Me	Me	12	C ₁₈ H ₄₂ Br ₂ N ₂
261300	-(CH ₂) ₄ -		10	C ₂₀ H ₄₂ Br ₂ N ₂

SOURCE – CNRS (Centre Natl. Rech. Sci.).

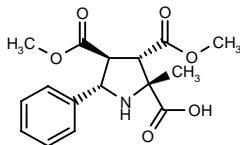
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261303

(2*R*,3*S*,4*S*,5*S*)-3,4-Bis(methoxycarbonyl)-2-methyl-5-phenyl-1*H*-pyrrole-2-carboxylic acid



C16-H19-N-O6; Mol wt: 321.33

ACTION – A selective inhibitor of heme oxygenase activity of *Plasmodium* parasites, as demonstrated both *in vitro* (100% inhibition at 10 μM in cell-free *Plasmodium yoelii*) and *in vivo* in mice infected with *P. yoelii* (100% inhibition at 15 mg/kg p.o. for 5 days), without affecting host enzyme. Potentially useful for reversing resistance to antimalarials such as chloroquine by increasing levels of heme/hemozoin in resistant malarial parasites.

SOURCE – Central Drug Res. Inst., Lucknow (IN).

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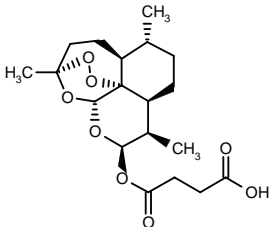
ARTESUNATE

Rec INN

091299

Succinic acid (3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,12-epoxy-3,6,9-trimethylperhydropyrano[4,3-*J*]-1,2-benzodioxepin-10-yl monoester

Plasmotrim®



C19-H28-O8; Mol wt: 384.43

ACTION – Antimalarial agent, a semisynthetic analog of artemisinin (qinghaosu) for i.v., i.m., oral or rectal administration. The compound has demonstrated high efficacy after oral administration in acute uncomplicated falciparum malaria, clear preventive effects in subjects from endemic areas, and high efficacy and good tolerance in severe malaria when given as suppositories followed by oral mefloquine. Artesunate appears to be well tolerated although neuropsychiatric side effects (nightmares, anxiety, restlessness and agitation, lack of concentration and dizziness) have been described during drug treatment, which may be related to its neurotoxic effects *in vitro* (IC₅₀ = 0.46 and 0.54 μM, respectively, in rat-derived neuroblastoma NG108-15 and mouse-derived neuroblastoma Neuro-2a cells). It is a potent and rapid-acting schizonticide under development for use in the treatment of severe malaria in regions of chloroquine- and multidrug-resistant *Plasmodium falciparum* malaria.

SOURCES – Guilin No. 2 Pharm. Factory (CN); Mepha Pharm.

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4. Batty, K.T. et al. Selective high-performance liquid chromatographic determination of artesunate and α- and β-dihydroartemisinin in patients with falciparum malaria. J Chromatogr B-Biomed Appl 1996, 677(2): 345.

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6. Benakis, A. et al. Pharmacokinetic study of a new pharmaceutical form of artesunate (Plasmotrim®-200 Rectocaps) administered in healthy volunteers by rectal route. 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-24-5.

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15. Jian, H.X. et al. *Effect of artesunate on the early stage of P. falciparum gametocyte (PFGe).* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst O-22-5.

16. Karbwang, J. et al. *Comparative clinical trial of artesunate and the combination of artesunate-mefloquine in multidrug-resistant falciparum malaria.* Clin Drug Invest 1996, 11(2): 84.

17. Klinnert, V. *Neuropsychiatric side effects in the treatment of falciparum malaria with artesunate.* Eur Conf Trop Med (Oct 22-26, Hamburg) 1995, Abst H74.

18. Li, G.Q. et al. *Effect of artesunate on the infectivity of P. falciparum gametocytes (PFG) and a randomized comparative study with quinine.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst O-22-4.

19. Li, G.Q. et al. *Field study of artesunate in prevention of malaria.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst O-20-6.

20. Lin, P.-Y. et al. *Effects of artesunate on immune function in mice.* Acta Pharmacol Sin 1995, 16(5): 441.

21. Looareesuwan, S. et al. *Efficacy and tolerability of a sequential, artesunate suppository-mefloquine, treatment of severe falciparum malaria.* Eur Conf Trop Med (Oct 22-26, Hamburg) 1995, Abst H81.

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23. Looareesuwan, S. et al. *Comparative clinical trial of a sequential, artesunate suppository followed by mefloquine, treatment of severe malaria.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-24-2.

24. Meyer, C.U. et al. *The antimalarial drug artesunate suppresses the T cell activation in human peripheral blood lymphocytes (PBL).* 36th Intersci Conf Antimicrob Agents Chemother (Sept 15-18, New Orleans) 1996, Abst G20.

25. Navaratnam, V. et al. *Comparative pharmacokinetic study of oral and rectal formulations of sodium artesunate in healthy volunteers.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst O-21-6.

26. Price, R.N. et al. *Adverse effects of artemisinin derivatives studied in 3645 patients.* Amer J Trop Med Hyg 1997, 57(3, Suppl.): Abst 5.

27. Sabchareon, A. et al. *Clinical and pharmacokinetic comparison of oral versus rectal artesunate in children with uncomplicated falciparum malaria.* Amer J Trop Med Hyg 1996, 55(2, Suppl.): Abst 2.

28. Sabchareon, A. et al. *Comparative clinical trial of artesunate suppositories and oral artesunate in combination with mefloquine in the treatment of children with acute falciparum malaria.* Amer J Trop Med Hyg 1998, 58(1): 11.

29. Teja-Isavadharm, P. et al. *Bioassay and HPLC measurement of sodium artesunate and its pharmacokinetics in uncomplicated falciparum malaria compared with healthy volunteers.* Amer J Trop Med Hyg 1996, 55(2, Suppl.): Abst 13.

30. Than, M. et al. *Clinical trial of artesunate and artemether suppositories (Rectocaps) in treatment of uncomplicated falciparum malaria.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-83-2.

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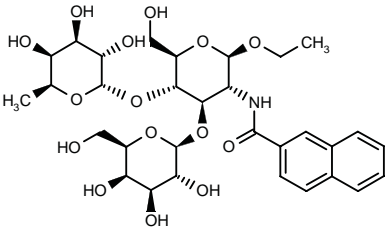
32. van Boxel, C.J. et al. *Some pharmacokinetic and dynamic comparisons of artemisinin derivatives in man.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst B-83-1.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

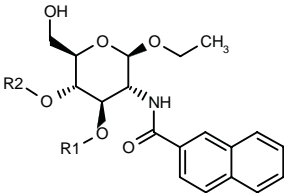
258451

Ethyl 2-deoxy-4-O-(6-deoxy-α-L-galactopyranosyl)-3-O-(β-D-galactopyranosyl)-2-(2-naphthylcarboxamido)-β-D-glucopyranoside



C31-H43-N-O15; Mol wt: 669.68

ACTION – Carbohydrate antiinflammatory agent whose activity was assessed in a teichoic acid-induced pleurisy model in mice (61.5% inhibition at 30 mg/kg i.v.). Other related compounds include the following:



Compound	R1	R2	Formula
261250	β-D-galactopyranosyl	6-deoxy-β-L-galactopyranosyl	C ₃₁ H ₄₃ NO ₁₅
261251	6-deoxy-β-L-galactopyranosyl	β-D-galactopyranosyl	C ₃₁ H ₄₃ NO ₁₅

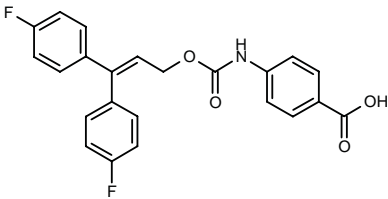
SOURCE – Sumitomo.

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258976

4-[3,3-Bis(4-fluorophenyl)allyloxycarbonylamino]benzoic acid



C23-H17-F2-N-O4; Mol wt: 409.39

10. Eamsila, C. et al. *Threat of malaria to military operations in Thailand; epidemiology and results of a pilot artesunate chemoprophylaxis study.* Amer J Trop Med Hyg 1997, 57(3, Suppl.): Abst 530.

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16. Karbwang, J. et al. *Comparative clinical trial of artesunate and the combination of artesunate-mefloquine in multidrug-resistant falciparum malaria.* Clin Drug Invest 1996, 11(2): 84.

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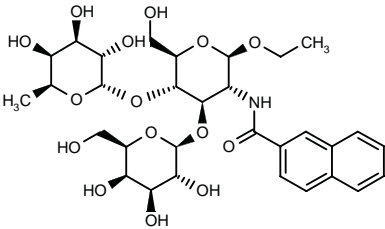
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

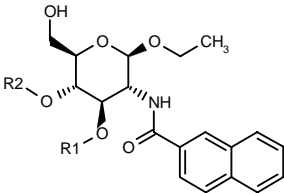
258451

Ethyl 2-deoxy-4-O-(6-deoxy-α-L-galactopyranosyl)-3-O-(β-D-galactopyranosyl)-2-(2-naphthylcarboxamido)-β-D-glucopyranoside



C31-H43-N-O15; Mol wt: 669.68

ACTION – Carbohydrate antiinflammatory agent whose activity was assessed in a teichoic acid-induced pleurisy model in mice (61.5% inhibition at 30 mg/kg i.v.). Other related compounds include the following:



Compound	R1	R2	Formula
261250	β-D-galactopyranosyl	6-deoxy-β-L-galactopyranosyl	C ₃₁ H ₄₃ NO ₁₅
261251	6-deoxy-β-L-galactopyranosyl	β-D-galactopyranosyl	C ₃₁ H ₄₃ NO ₁₅

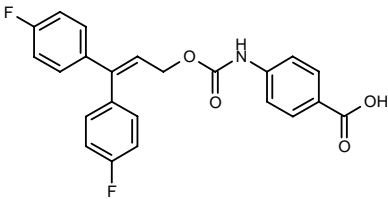
SOURCE – Sumitomo.

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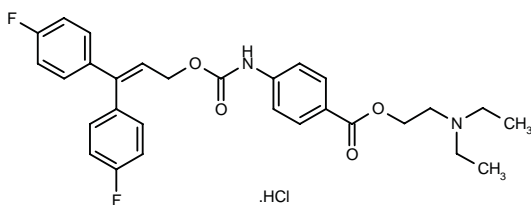
258976

4-[3,3-Bis(4-fluorophenyl)allyloxycarbonylamino]benzoic acid



C23-H17-F2-N-O4; Mol wt: 409.39

ACTION – Agent for the treatment of inflammatory and immune disorders such as rheumatoid arthritis that acts by inhibiting the production of IL-1 β , as demonstrated both *in vitro* (51.6% inhibition of lipopolysaccharide [LPS]-induced IL-1 β production in human monocytes at 10 μ M) and *in vivo* (84.1% inhibition of carrageenan-induced IL-1 β production in mice at 100 mg/kg p.o.). It was active against carrageenan-induced paw edema (43% inhibition at 100 mg/kg p.o.) and adjuvant-induced arthritis (45% inhibition at 100 mg/kg p.o.) in rats and proved effective in a collagen-induced model of arthritis in mice at 30 and 100 mg/kg p.o. In addition, it inhibited the reverse passive Arthus reaction in rats (32% inhibition at 100 mg/kg p.o.) and was effective in a rabbit anti-Thy-1 antibody-induced nephritis model in rats (76% inhibition at 100 mg/kg p.o.); 38% inhibition of acetylcholine-induced bronchial hyperreactivity was observed in rats at a dose of 30 mg/kg s.c. No mortality was observed following p.o. administration of up to 1000 mg/kg to mice and rats. Another exemplified substituted ethylene compound is:



261822: C29-H30-F2-N2-O4.HCl

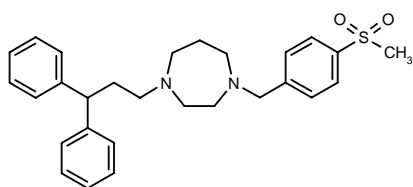
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259045

1-(3,3-Diphenylpropyl)-4-[4-(methylsulfonyl)benzyl]-hexahydro-1,4-diazepine



C28-H34-N2-O2-S; Mol wt: 462.65

ACTION – Agent for the treatment of atherosclerosis and rheumatoid arthritis and other disorders characterized by tissue infiltration by monocytes and lymphocytes, a chemokine receptor antagonist that inhibits the action of chemokines such as IL-8, macrophage inflammatory protein-1 α (MIP-1 α) and monocyte chemotactic protein-1 (MCP-1, also known as MCAF or macrophage chemotactic and activating factor) on target cells. In *in vitro* studies measuring the inhibition of [125 I]-labeled human MCP-1 binding to cells expressing the MCP-1 receptor, it gave an IC₅₀ value of 17 μ M. Compound was also tested for inhibition of cell chemotaxis caused by MCP-1 using the human monocytic leukemia cell line THP-1 as the chemotactic cell (IC₅₀ = 9 μ M). It exhibited significant inhibitory activity in a mouse model of DNFB-induced contact hypersensitivity when given topically.

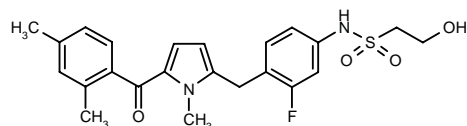
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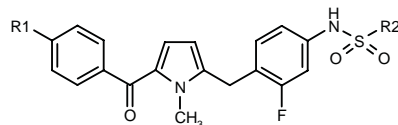
260061

N-[4-[5-(2,4-Dimethylbenzoyl)-1-methylpyrrol-2-ylmethyl]-3-fluorophenyl]-2-hydroxyethanesulfonamide

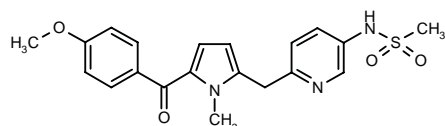


C23-H25-F-N2-O4-S; Mol wt: 444.52

ACTION – Antiinflammatory agent with potent and selective inhibitory activity against cyclooxygenase type 2 (COX-2) as compared to type 1 isozyme (COX-1). Antiinflammatory activity was evaluated in the carrageenan-induced paw edema test in rats in which it produced 35% inhibition at 10 mg/kg p.o. Inhibition of eicosanoid synthesis *in vivo* was also evaluated, with 64% inhibition of air pouch PGE₂ formation in rats at a dose of 30 mg/kg p.o. (indomethacin: > 70% inhibition at 2-5 mg/kg p.o.). Other specifically claimed pyrrole derivatives include the following:



Compound	R1	R2	Formula
260726	Me	CH ₂ CH ₂ OH	C ₂₂ H ₂₃ FN ₂ O ₄ S
260727	H	CH ₂ CH ₂ OH	C ₂₁ H ₂₁ FN ₂ O ₄ S
260728	H	NH ₂	C ₁₉ H ₁₈ FN ₂ O ₃ S



260729: C20-H21-N3-O4-S

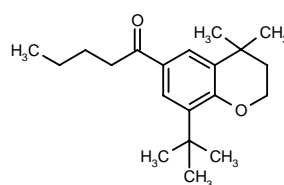
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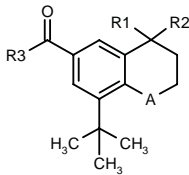
260066

1-(8-*tert*-Butyl-4,4-dimethyl-3,4-dihydro-2H-1-benzopyran-6-yl)-1-pentaone



C20-H30-O2; Mol wt: 302.46

ACTION – Nonsteroidal antiinflammatory and analgesic agent reported to exhibit reduced gastrointestinal side effects compared to other nonsteroidal antiinflammatory drugs (NSAIDs). Othe exemplified dihydrobenzopyran and related compounds include the following:



Compound	R1=R2	R3	A	Formula
261175	Me	cyclopropyl-(CH2)3	O	C ₂₂ H ₃₂ O ₂
261176	Me	CH2C(Me)2OH	O	C ₂₀ H ₃₀ O ₃
261177	H	CH2C(Me)2OH	O	C ₁₈ H ₂₆ O ₃
261178	H	CH=C(Me)2	O	C ₁₈ H ₂₄ O ₂
261179	H	CH2C(Me)2Cl	O	C ₁₈ H ₂₅ ClO ₂
261180	Me	Bu	S	C ₂₀ H ₃₀ OS
261181	Me	3-THF	S	C ₂₀ H ₂₈ O ₂ S

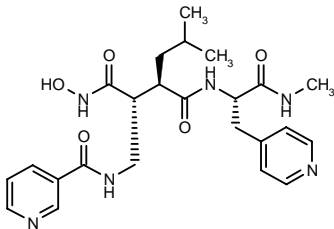
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260101

N-[4-(Hydroxyamino)-2(*R*)-isobutyl-3-(3-pyridylcarbox-amidomethyl)succinyl]-L-(4-pyridyl)alanine methylamide



C24-H32-N6-O5; Mol wt: 484.55

ACTION – An inhibitor of the production of tumor necrosis factor- α (TNF- α) and the activity of matrix metallo-proteinases (MMPs) such as human collagenase (IC₅₀ = 1.5 nM against human enzyme from IL-1 β -stimulated human skin fibroblasts) from a series of succinamide derivatives, potentially useful in the treatment of disorders such as rheumatoid arthritis, cancer, restenosis, psoriasis, stroke and septic shock.

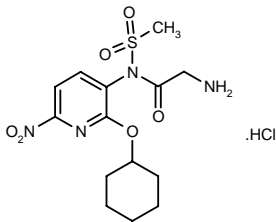
SOURCE – Fujisawa.

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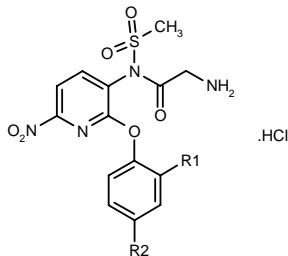
260102

N¹-(2-Cyclohexyloxy-6-nitropyridin-3-yl)-N¹-(meth-anesulfonyl)glycinamide hydrochloride



C14-H20-N4-O6-S.HCl; Mol wt: 408.86

ACTION – Antiinflammatory and analgesic agent reported to exhibit minimal gastrointestinal side effects and shown to inhibit carrageenan-induced paw edema in rats following oral administration (48.2% inhibition at 1 mg/kg p.o.). Other compounds from this series of 6-nitropyridine-sulfonamides include the following:



Compound	R1=R2	Formula
261393	H	C ₁₄ H ₁₄ N ₄ O ₆ S.HCl
261394	F	C ₁₄ H ₁₂ F ₂ N ₄ O ₆ S.HCl

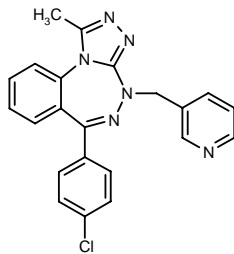
SOURCE – Taisho.

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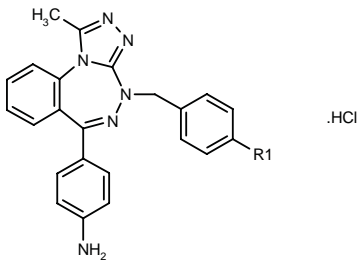
260109

6-(4-Chlorophenyl)-1-methyl-4-(3-pyridylmethyl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,3,4]benzotriazepine

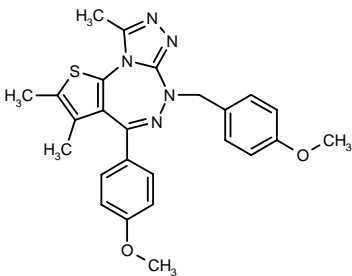


C22-H17-Cl-N6; Mol wt: 400.87

ACTION – Antiinflammatory agent, an inhibitor of the production of cytokines such as IL-8 ($IC_{50} = 0.26 \mu M$), GM-CSF ($IC_{50} = 0.05 \mu M$), IL-2 ($IC_{50} = 0.24 \mu M$) and interferon gamma ($IC_{50} = 0.12 \mu M$). *In vivo*, it gave 51% inhibition of lipopolysaccharide (LPS)-stimulated tumor necrosis factor- α (TNF- α) production in the plasma of mice at 30 mg/kg p.o. Antiinflammatory activity was demonstrated in the adjuvant-induced arthritis test in rats ($72.7 \pm 3.3\%$ inhibition at 10 mg/kg/day p.o. x 28 days). Other compounds from this series of triazepine derivatives include the following:



Compound	R1	Formula
261940	Cl	C ₂₃ H ₁₉ ClN ₆ .HCl
261941	NO2	C ₂₃ H ₁₉ N ₇ O ₂ .HCl



261939: C₂₅-H₂₅-N₅-O₂-S

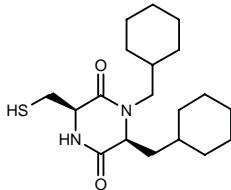
SOURCE – Japan Tobacco.

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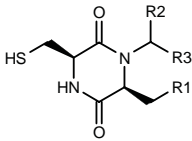
260124

(3*R*,6*S*)-1,6-Bis(cyclohexylmethyl)-3-(sulfanylmethyl)-piperazine-2,5-dione



C₁₉-H₃₂-N₂-O₂-S; Mol wt: 352.53

ACTION – Agent for the treatment of diseases involving tissue degradation such as rheumatoid arthritis that acts by inhibiting matrix metalloproteinases. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
261259	cyclohexyl	H	4-MeO-Ph	C ₂₀ H ₂₈ N ₂ O ₃ S
261260	4-NO ₂ -Ph	H	2-quinoliny	C ₂₂ H ₂₀ N ₄ O ₄ S
261261	4-NO ₂ -Ph	H	4-MeO-Ph	C ₂₀ H ₂₁ N ₃ O ₅ S
261262	4-NO ₂ -Ph	Et	cyclohexyl-NHCO	C ₂₂ H ₃₀ N ₄ O ₅ S
261263	4-NO ₂ -Ph	H	cyclohexyl-NHCO	C ₂₀ H ₂₆ N ₄ O ₅ S

SOURCE – Glaxo Wellcome.

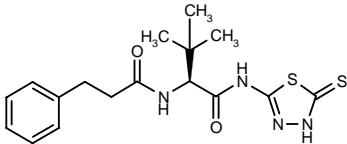
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260126

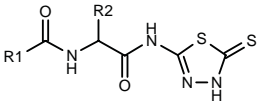
*N*²-(3-Phenylpropionyl)-*N*¹-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-L-*tert*-leucinamide

3-Methyl-*N*²-(3-phenyl-propionyl)-*N*¹-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-L-valinamide



C₁₇-H₂₂-N₄-O₂-S₂; Mol wt: 378.51

ACTION – An inhibitor of matrix metalloproteinases, particularly stromelysin ($K_i = 0.24 \mu M$), with potential in the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, tumor metastasis, periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation and other diseases related to connective tissue degradation. Other compounds from this series of thiadiazole amide derivatives include the following:



Compound	R1	R2	Isomer	Formula
260952	9-fluorenyl-CH ₂ O	(S)-CH(Me)Et	L	C ₂₃ H ₂₄ N ₄ O ₃ S ₂
260953	OCH ₂ Ph	t-Bu	L	C ₁₆ H ₂₀ N ₄ O ₃ S ₂
260954	OCH ₂ Ph	cyclohexyl	L	C ₁₈ H ₂₂ N ₄ O ₃ S ₂
260955	CH ₂ CH ₂ Ph	Ph	DL	C ₁₉ H ₁₈ N ₄ O ₂ S ₂
260956	CH ₂ OCH ₂ Ph	Ph	DL	C ₁₉ H ₁₈ N ₄ O ₃ S ₂
260957	(F)5-PhCH ₂ CH ₂	t-Bu	L	C ₁₇ H ₁₇ F ₅ N ₄ O ₂ S ₂

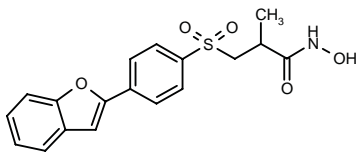
SOURCE – Pharmacia & Upjohn.

REFERENCES

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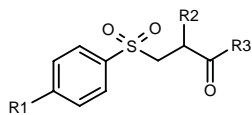
260179

3-[4-(Benzofuran-2-yl)phenylsulfonyl]-2-methylpropiono-hydroxamic acid



C18-H17-N-O5-S; Mol wt: 359.40

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, arterio-sclerosis, pulmonary emphysema, hepatic cirrhosis, corneal injury, autoimmune diseases and neo-vascularization that acts by inhibiting matrix metalloproteinases (MMPs) such as gelatinase A (IC₅₀ = 0.0014 μM against enzyme purified from human skin fibroblasts). Other compounds from this series of aryl (sulfide, sulfoxide and sulfone) derivatives include the following:



Compound	R1	R2	R3	Formula
261239	NHCOPh	H	OH	C ₁₆ H ₁₅ NO ₅ S
261240	Ph-ethynylene	H	OH	C ₁₇ H ₁₄ O ₄ S
261241	OMe	t-BuOCONH-CH(Ph)CONH	NHOH	C ₂₃ H ₂₉ N ₃ O ₆ S
261242	C5H11-ethynylene	Me	NHOH	C ₁₇ H ₂₃ NO ₄ S
261243	4-Me-Ph-ethynylene	Me	NHOH	C ₁₉ H ₁₉ NO ₄ S

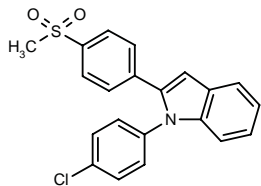
SOURCE – Ono.

REFERENCES

1. Takahashi, K. and Sugiura, T. (Ono Pharm. Co., Ltd.) *Aryl (sulfide, sulfoxide and sulfone) derivs. and drugs containing the same as the active ingredient.* WO 9749679.

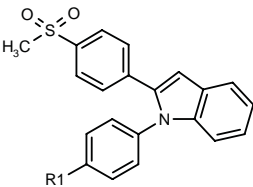
260766

1-(4-Chlorophenyl)-2-[4-(methylsulfonyl)phenyl]indole



C21-H16-Cl-N-O2-S; Mol wt: 381.88

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; 95% inhibition at 10 μM using enzyme purified from sheep placenta). No toxicity was observed following administration of up to 300 mg/kg p.o. to rats. Other specifically claimed compounds from this series of 1,2-diarylindole derivatives include the following:



Compound	R1	Formula
261062	F	C ₂₁ H ₁₆ FNO ₂ S
261063	Me	C ₂₂ H ₁₉ NO ₂ S
261064	H	C ₂₁ H ₁₇ NO ₂ S

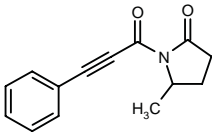
SOURCE – UPSA.

REFERENCES

1. Güngör, T. and Teulon, J.-M. (Labs. UPSA) *1,2-Diarylindole derivs., processes for their preparation and their uses in therapeutics.* US 5723485.

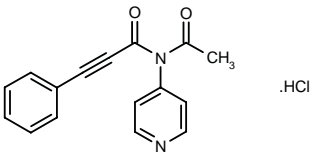
260860

5-Methyl-1-(3-phenyl-2-propynoyl)pyrrolidin-2-one



C14-H13-N-O2; Mol wt: 227.26

ACTION – Agent for the treatment of rheumatoid arthritis, sepsis, ulcerative colitis and Crohn's disease, an inhibitor of the production of IL-1β (IC₅₀ = 2.8 μM using THP-1 cells derived from human peripheral blood) and tumor necrosis factor (TNF-α; IC₅₀ = 0.9 μM). Compound exhibited relatively low cytotoxicity against THP-1 cells, giving an LD₅₀ value of 110 μM. *In vivo*, it gave 29% inhibition of lipopolysaccharide (LPS)-induced TNF-α production in mice at 10 mg/kg i.p. Another compound from this series of imide derivatives is:



261272: C16-H12-N2-O2.HCl

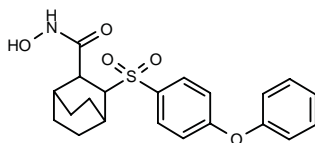
SOURCE – Nisshin Flour Milling.

REFERENCES

1. Yokoyama, S. et al. (Nisshin Flour Milling Co., Ltd.) *Imide derivs.* EP 818439, JP 98072421.

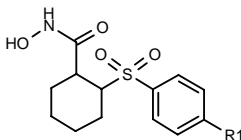
260861

3-(4-Phenoxybenzenesulfonyl)bicyclo[2.2.2]octane-2-carboxylic acid



C21-H23-N-O5-S; Mol wt: 401.48

ACTION – An inhibitor of matrix metalloproteinases (MMPs) and the production of tumor necrosis factor (TNF) with potential in the treatment of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, as well as AIDS, sepsis and other diseases characterized by MMP activity and/or involving the production of TNF. A representative compound from a series of cyclic sulfone derivatives, wherein the following are also included:



Compound	R1	Formula
261395	OMe	C ₁₄ H ₁₉ NO ₅ S
261396	1,3-dioxo-2-isoindolyl-CH ₂ CH ₂ O	C ₂₃ H ₂₄ N ₂ O ₇ S
261397	OCH ₂ Ph	C ₂₀ H ₂₃ NO ₅ S
261398	4-MeO-Ph(CH ₂) ₃ O	C ₂₃ H ₂₉ NO ₆ S
261399	6-MeO-3-Pyr	C ₁₉ H ₂₂ N ₂ O ₅ S
261400	Br	C ₁₃ H ₁₆ BrNO ₄ S

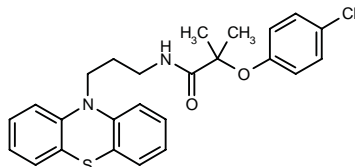
SOURCE – Pfizer.

REFERENCES

- Burgess, L.E. et al. (Pfizer, Inc.) *Cyclic sulphone derivs. as inhibitors of metalloproteinases and of the production of tumor necrosis factor*. EP 818442.

261134

2-(4-Chlorophenoxy)-N-[3-(phenothiazin-10-yl)propyl]-2-methylpropanamide



C25-H25-Cl-N2-O2-S; Mol wt: 453.00

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 1.3 μM vs. IC₅₀ > 50 μM for COX-1) with a novel structure discovered using a combination of computational 3-D database searching and combinatorial chemistry. Although its selectivity is less than that of known COX-2 inhibitors, it may be useful as a lead compound for the development of novel antiinflammatory agents.

SOURCE – Abbott.

REFERENCES

- Stewart, K.D. et al. *Discovery of a new cyclooxygenase-2 lead compound through 3-D database searching and combinatorial chemistry*. Bioorg Med Chem Lett 1998, 8(5): 529.

ENBREL™

213242

Recombinant fusion protein comprising the soluble human p75 tumor necrosis factor (TNF) receptor linked to the Fc portion of human IgG₁

TNR-001

TNFR:Fc

Recombinant human TNFR p75-Fc fusion protein

ACTION – Recombinant human soluble tumor necrosis factor-α receptor (rhTNFR) fusion protein proven effective and safe in the treatment of active rheumatoid arthritis in double-blind, placebo-controlled clinical studies. It competitively inhibits the binding of TNF to its cell-surface receptors, thereby inhibiting the biological activity of TNF. Enbrel™ was designated a fast track product by the FDA and BLA filing has been completed. Other potential indications for the product include heart failure and coronary artery disease.

SOURCES – Immunex; Wyeth-Ayerst.

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20. *Favorable results obtained with Enbrel combination in RA*. Prous Science Daily Essentials March 16, 1998.

21. *Immunex reports first quarter results - Research investment up 21 percent as company prepares new drugs for clinical trials*. Immunex Corp. Press Release 1996, March 31.

22. *Immunex reports second quarter results. Revenues up in first half; new research agreement to reduce expenses*. Immunex Corp. Press Release 1996, July 18.

23. *Immunex reports third quarter results - Operating efficiencies improve bottom line*. Immunex Corp. Press Release 1994, October 18.

24. *Immunex's ENBREL demonstrates positive safety profile in RA patients*. Prous Science Daily Essentials April 14, 1997.

25. *Long-term ENBREL safe and effective in RA*. Prous Science Daily Essentials June 11, 1997.

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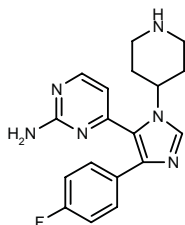
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30. *Wyeth-Ayerst to promote Immunex's ENBREL in U.S.* Prous Science Daily Essentials October 3, 1997.

SB-220025

260502

4-[4-(4-Fluorophenyl)-1-(4-piperidinyl)-1H-imidazol-5-yl]-pyrimidine-2-amine



C18-H19-F-N6; Mol wt: 338.39

ACTION – Agent for the treatment of chronic proliferative inflammatory diseases such as rheumatoid arthritis, a member of the CSAIDTM class of cytokine biosynthesis inhibitors that inhibits pathological angiogenesis and the synthesis of proinflammatory cytokines such as IL-1 β and tumor necrosis factor- α (TNF- α), through specific

inhibition of p38 mitogen-activated protein (MAP) kinase (IC_{50} = 60 nM). In mice, it inhibited lipopolysaccharide (LPS)-induced TNF- α production with an ED_{50} of 7.5 mg/kg p.o. Activity was demonstrated in the air pouch granuloma model of inflammatory angiogenesis in mice, producing a maximum 44% reduction in angiogenesis at 50 mg/kg/day p.o. on day 6, which was correlated with reductions in TNF- α and IL-1 β levels. It was also shown to prevent the progression of established arthritis in a murine collagen-induced arthritis model at a dose of 50 mg/kg b.i.d. p.o.

SOURCE – SmithKline Beecham.

REFERENCES

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4. Sisko, J. (SmithKline Beecham Corp.) *Novel synthesis*. WO 9723479.

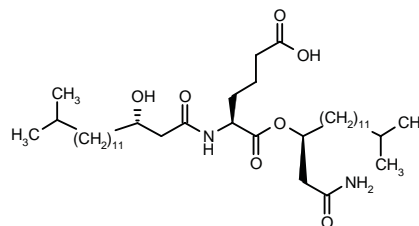
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6. Winkler, J.D. et al. *Inhibition of angiogenesis by SB 220025, a selective inhibitor of p38 MAP kinase*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1853.

WA-8242B

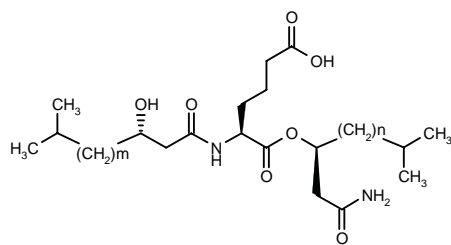
259698

2(S)-[3(S)-Hydroxy-15-methylhexadecanamido]-hexanedioic acid 1-[1(S)-(carbamoylmethyl)-13-methyl-tetradecyl] monoester



C40-H76-N2-O7; Mol wt: 697.05

ACTION – Selective inhibitor of secretory phospholipase A₂ (sPLA₂) obtained from the cultured mycelium of *Streptomyces violaceusniger* No. 8242; it concentration-dependently inhibited group I (porcine pancreatic) and group II (recombinant human synovial) sPLA₂, with respective IC_{50} values using pyrene-labeled phosphatidylethanolamine and pyrene-labeled phosphatidylcholine of 0.14 and 1.1 nM; it behaved as a competitive inhibitor of group II enzyme (K_i = 0.254 ng/ml). WA-8242B concentration-dependently inhibited PGI₂ production in human umbilical vein endothelial cells (HUVEC) induced by tumor necrosis factor (TNF- α), group II sPLA₂ and TNF- α + group II sPLA₂ (IC_{50} = 8.4 μ g/ml against the latter). Dose-dependent activity was also observed in the zymosan-induced writhing test in mice (ED_{50} = 5.6 mg/kg i.p.). Other related compounds also considered to be promising candidates as novel nonsteroidal antiinflammatory and antiallergic drugs are:



Compound	m	n	Formula
WA-8242A1 [259696]	11	10	C ₃₉ H ₇₄ N ₂ O ₇
WA-8242A2 [259697]	10	11	C ₃₉ H ₇₄ N ₂ O ₇

SOURCE – Fujisawa.

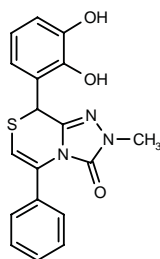
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3. Yoshimura, S. et al. WA8242A1, A₂ and B, novel secretory phospholipase A₂ inhibitors produced by *Streptomyces violaceusniger*. I. Taxonomy, production and purification. J Antibiot 1998, 51(1): 1.

IMMUNOLOGIC DRUGS

258450

8-(2,3-Dihydroxyphenyl)-5-phenyl-2-methyl-3,8-dihydro-2H-1,2,4-triazolo[3,4-c][1,4]thiazin-3-one



C18-H15-N3-O3-S; Mol wt: 353.39

ACTION – Agent for the treatment of allergy, autoimmune diseases, transplant rejection or graft-vs.-host disease shown to inhibit T-cell activation and the production of IL-5 and interferon gamma in mouse spleen cells.

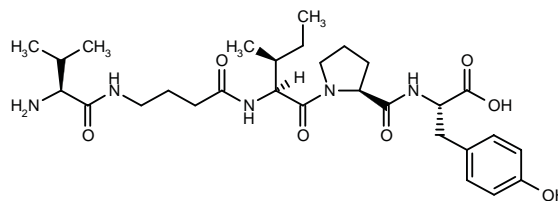
SOURCE – Takeda.

REFERENCES

1. Furuya, S. et al. (Takeda Chem. Ind., Ltd.) *Condensed thiazine derivs., preparation method thereof and their use*. JP 97301980.

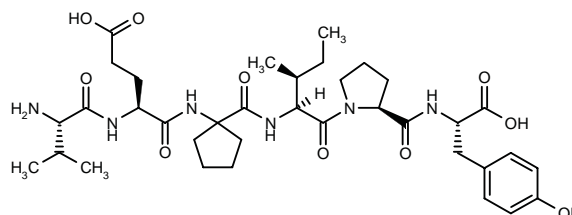
260756

L-Valyl-4-aminobutanoyl-L-isoleucyl-L-prolyl-L-tyrosine



C29-H45-N5-O7; Mol wt: 575.70

ACTION – Human β -casein fragment (54-59) analog with significant immunosuppressant effect in the mouse lymphocyte transformation (LTT) and mixed lymphocyte reaction (MLR) tests. Along with the compound shown below, it is suggested to qualify as a lead molecule for optimization in the search for low-molecular-weight immunosuppressants.



259664: C36-H54-N6-O10

SOURCE – Central Drug Res. Inst., Lucknow (IN).

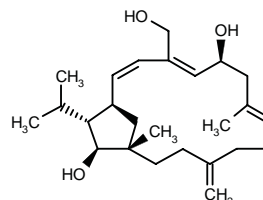
REFERENCES

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KOBIIN

260814

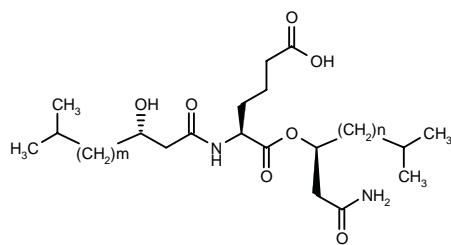
(2R,3R,3aR,4Z,6Z,8S,10E,16aR)-6-(Hydroxymethyl)-3-isopropyl-10,16a-dimethyl-14-methylene-1,2,3,3a,8,9,12,13,14,15,16,16a-dodecahydrocyclopentacyclopentadecene-2,8-diol



C25-H40-O3; Mol wt: 388.59

Pale yellow oil, $[\alpha]_D^{22} +41.2^\circ$ (c 0.25, CHCl₃).

ACTION – Sesterterpenetriol that constitutes the major immunosuppressive component of the fungus *Gelasino-spora kobei*. IC₅₀ values of 7.0 and 3.5 μ g/ml, respectively, were calculated for inhibition of concanavalin A (Con A)- and lipopolysaccharide (LPS)-induced proliferation of mouse spleen lymphocytes. Another immunosuppressive component of this fungus is:



Compound	m	n	Formula
WA-8242A1 [259696]	11	10	C ₃₉ H ₇₄ N ₂ O ₇
WA-8242A2 [259697]	10	11	C ₃₉ H ₇₄ N ₂ O ₇

SOURCE – Fujisawa.

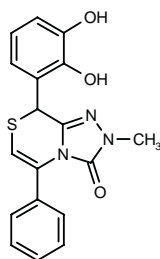
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IMMUNOLOGIC DRUGS

258450

8-(2,3-Dihydroxyphenyl)-5-phenyl-2-methyl-3,8-dihydro-2H-1,2,4-triazolo[3,4-c][1,4]thiazin-3-one



C18-H15-N3-O3-S; Mol wt: 353.39

ACTION – Agent for the treatment of allergy, autoimmune diseases, transplant rejection or graft-vs.-host disease shown to inhibit T-cell activation and the production of IL-5 and interferon gamma in mouse spleen cells.

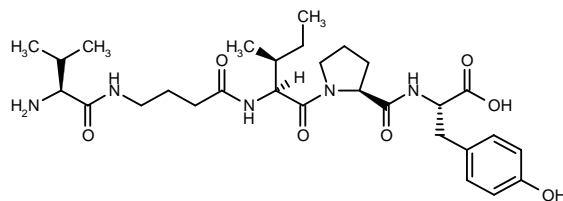
SOURCE – Takeda.

REFERENCES

1. Furuya, S. et al. (Takeda Chem. Ind., Ltd.) *Condensed thiazine derivs., preparation method thereof and their use*. JP 97301980.

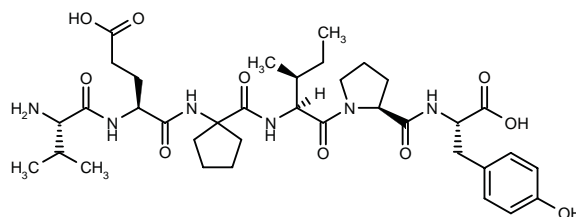
260756

L-Valyl-4-aminobutanoyl-L-isoleucyl-L-prolyl-L-tyrosine



C29-H45-N5-O7; Mol wt: 575.70

ACTION – Human β-casein fragment (54-59) analog with significant immunosuppressant effect in the mouse lymphocyte transformation (LTT) and mixed lymphocyte reaction (MLR) tests. Along with the compound shown below, it is suggested to qualify as a lead molecule for optimization in the search for low-molecular-weight immunosuppressants.



259664: C36-H54-N6-O10

SOURCE – Central Drug Res. Inst., Lucknow (IN).

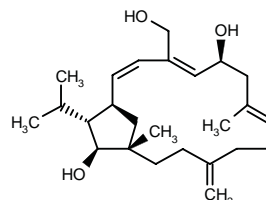
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KOBIIN

260814

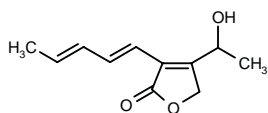
(2R,3R,3aR,4Z,6Z,8S,10E,16aR)-6-(Hydroxymethyl)-3-isopropyl-10,16a-dimethyl-14-methylene-1,2,3,3a,8,9,12,13,14,15,16,16a-dodecahydrocyclopentacyclopentadecene-2,8-diol



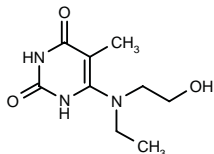
C25-H40-O3; Mol wt: 388.59

Pale yellow oil, [α]_D²² +41.2° (c 0.25, CHCl₃).

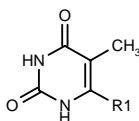
ACTION – Sesterterpenetriol that constitutes the major immunosuppressive component of the fungus *Gelasinospora kobei*. IC₅₀ values of 7.0 and 3.5 μg/ml, respectively, were calculated for inhibition of concanavalin A (Con A)- and lipopolysaccharide (LPS)-induced proliferation of mouse spleen lymphocytes. Another immunosuppressive component of this fungus is:

**Kobifuranone B [260815]:** C₁₁-H₁₄-O₃**SOURCE** – Chiba Univ., Chiba (JP).**REFERENCES**

1. Fujimoto, H. et al. *Four new immunosuppressive components, kobilin and kobifuranones A, B, and C, from an ascomycete, Gelasinospora kobilii*. Chem Pharm Bull 1998, 46(2): 211.
2. Fujimoto, H. et al. *New immunosuppressive components from ascomycetes, Diplogelasinospora grovesii and a related fungus*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1996, 38: 621.
3. Fujimoto, H. et al. *New immunosuppressive components from ascomycetes Gelasinospora multiforis and Gelasinospora kobilii*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1995, 37: 625.

ONCOLYTIC DRUGS**ANTIMETABOLITES****260537**6-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]thymine6-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]-5-methyluracilC₉-H₁₅-N₃-O₃; Mol wt: 213.24

ACTION – Water-soluble antineoplastic and anti-angiogenic agent, an inhibitor of thymidine phosphorylase (IC₅₀ < 0.02 μM against enzyme from *Escherichia coli*), shown to inhibit cell migration and neovascularization in human umbilical vein endothelial cells (HUVEC). Other compounds from this series of 6-amino-5-methyluracil derivatives include the following:



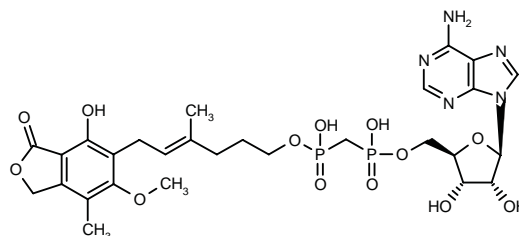
Compound	R1	Formula
261450	NHCH ₂ CH ₂ OH	C ₇ H ₁₁ N ₃ O ₃
261451	4-Me-1-Piz	C ₁₀ H ₁₆ N ₄ O ₂
261452	NH(CH ₂) ₃ OH	C ₈ H ₁₃ N ₃ O ₃
261453	NHCH ₂ CH(OH)CH ₂ OH	C ₈ H ₁₃ N ₃ O ₄

SOURCE – Mitsui Toatsu.**REFERENCES**

1. Fukazawa, N. et al. (Mitsui Toatsu Chem., Inc.) *6-Amino-5-methyluracil derivs.* JP 98017555.

260689

Methylenebisphosphonic acid *P*¹-(adenosine-5'-*O*-yl) monoester *P*²-[6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4(*E*)-hexen-1-yl] monoester

C₂₈-H₃₇-N₅-O₁₃-P₂; Mol wt: 713.57

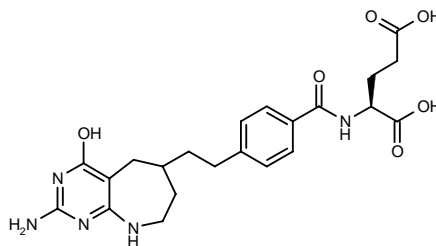
ACTION – Potent IMP (inosine monophosphate) dehydrogenase (IMPDH) type II inhibitor (K_i = 0.3 μM for human enzyme), an analog of mycophenolic adenine dinucleotide shown to potently inhibit the growth of human erythroleukemia K562 cells (IC₅₀ = 1.5 μM) and induce differentiation of 84.3 and 91.0% of cells at concentrations of 5 and 10 μM, respectively. In contrast to mycophenolic acid or mycophenolic alcohol, it is not converted to glucuronide in the presence of uridine 5'-diphosphoglucuronyl-transferase and is resistant to phosphodiesterases.

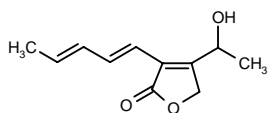
SOURCE – Codon Pharm.**REFERENCES**

1. Lesiak, K. et al. *Synthesis of a methylenebis(phosphonate) analogue of mycophenolic adenine dinucleotide: A glucuronidation-resistant MAD analogue of NAD.* J Med Chem 1998, 41(4): 618.

261166

N-[4-[2-(2-Amino-4-hydroxy-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepin-6-yl)ethyl]benzoyl]-L-glutamic acid

C₂₂-H₂₇-N₅-O₆; Mol wt: 457.49



Kobifuranone B [260815]: C₁₁-H₁₄-O₃

SOURCE – Chiba Univ., Chiba (JP).

REFERENCES

1. Fujimoto, H. et al. *Four new immunosuppressive components, kobilin and kobifuranones A, B, and C, from an ascomycete, Gelasinospora kobilii*. Chem Pharm Bull 1998, 46(2): 211.
2. Fujimoto, H. et al. *New immunosuppressive components from ascomycetes, Diplogelasinospora grovesii and a related fungus*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1996, 38: 621.
3. Fujimoto, H. et al. *New immunosuppressive components from ascomycetes Gelasinospora multiforis and Gelasinospora kobilii*. Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1995, 37: 625.

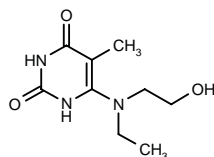
ONCOLYTIC DRUGS

ANTIMETABOLITES

260537

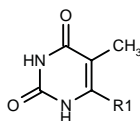
6-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]thymine

6-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]-5-methyluracil



C₉-H₁₅-N₃-O₃; Mol wt: 213.24

ACTION – Water-soluble antineoplastic and anti-angiogenic agent, an inhibitor of thymidine phosphorylase (IC₅₀ < 0.02 μM against enzyme from *Escherichia coli*), shown to inhibit cell migration and neovascularization in human umbilical vein endothelial cells (HUVEC). Other compounds from this series of 6-amino-5-methyluracil derivatives include the following:



Compound	R1	Formula
261450	NHCH ₂ CH ₂ OH	C ₇ H ₁₁ N ₃ O ₃
261451	4-Me-1-Piz	C ₁₀ H ₁₆ N ₄ O ₂
261452	NH(CH ₂) ₃ OH	C ₈ H ₁₃ N ₃ O ₃
261453	NHCH ₂ CH(OH)CH ₂ OH	C ₈ H ₁₃ N ₃ O ₄

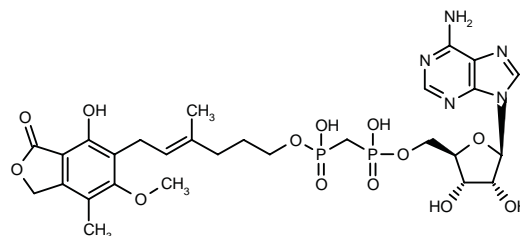
SOURCE – Mitsui Toatsu.

REFERENCES

1. Fukazawa, N. et al. (Mitsui Toatsu Chem., Inc.) *6-Amino-5-methyluracil derivs.* JP 98017555.

260689

Methylenebisphosphonic acid *P*¹-(adenosine-5'-*O*-yl) monoester *P*²-[6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4(*E*)-hexen-1-yl] monoester



C₂₈-H₃₇-N₅-O₁₃-P₂; Mol wt: 713.57

ACTION – Potent IMP (inosine monophosphate) dehydrogenase (IMPDH) type II inhibitor (K_i = 0.3 μM for human enzyme), an analog of mycophenolic adenine dinucleotide shown to potently inhibit the growth of human erythroleukemia K562 cells (IC₅₀ = 1.5 μM) and induce differentiation of 84.3 and 91.0% of cells at concentrations of 5 and 10 μM, respectively. In contrast to mycophenolic acid or mycophenolic alcohol, it is not converted to glucuronide in the presence of uridine 5'-diphosphoglucuronyl-transferase and is resistant to phosphodiesterases.

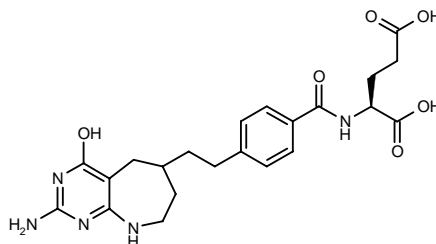
SOURCE – Codon Pharm.

REFERENCES

1. Lesiak, K. et al. *Synthesis of a methylenebis(phosphonate) analogue of mycophenolic adenine dinucleotide: A glucuronidation-resistant MAD analogue of NAD*. J Med Chem 1998, 41(4): 618.

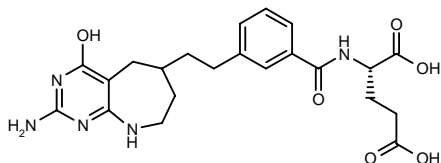
261166

N-[4-[2-(2-Amino-4-hydroxy-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepin-6-yl)ethyl]benzoyl]-L-glutamic acid

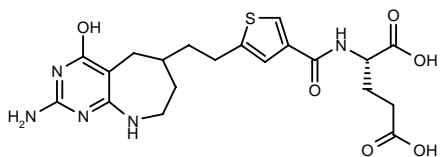


C₂₂-H₂₇-N₅-O₆; Mol wt: 457.49

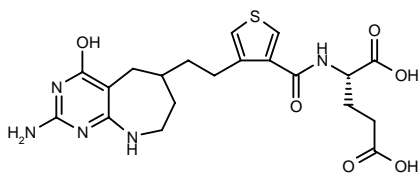
ACTION – Antineoplastic agent with strong inhibitory activity against the enzyme phosphoribosylglycinamide formyltransferase (glycinamide ribonucleotide formyltransferase; $IC_{50} = 0.047 \mu M$); it inhibited the growth of human T-cell-derived lymphoblastic leukemia CCRF-CEM cells with an IC_{50} of $0.047 \mu g/ml$. Also reported to be useful in the treatment of arthritis. Other specifically claimed 5,6,7,8-tetrahydropyrimidino[4,5-*b*]azepine derivatives include the following:



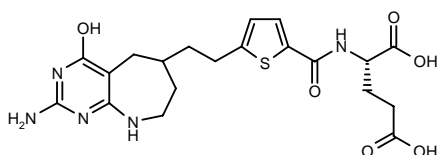
262198: C22-H27-N5-O6



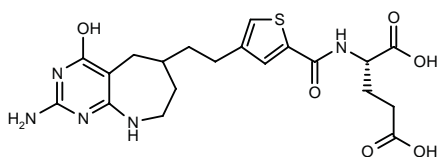
262199: C20-H25-N5-O6-S



262200: C20-H25-N5-O6-S



262201: C20-H25-N5-O6-S



262202: C20-H25-N5-O6-S

SOURCE – Princeton Univ., Princeton, NJ (US).

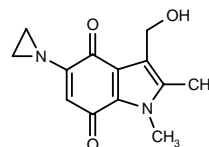
REFERENCES

1. Taylor, E.C. and Dowling, J.E. (Trustees Princeton Univ.) 5,6,7,8-Tetrahydropyrimido[4,5-*b*]azepine derivs. WO 9800426.

DNA-DAMAGING DRUGS

251661

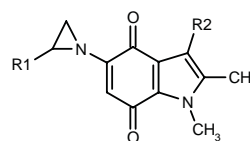
5-(Aziridin-1-yl)-3-(hydroxymethyl)-1,2-dimethyl-4,7-dihydro-1*H*-indole-4,7-dione



C13-H14-N2-O3; Mol wt: 246.27

Dark red solid, m.p. 173-4 °C (decomp.).

ACTION – Cytotoxic agent, a bioreductive alkylating agent with selectivity for hypoxic cells, as demonstrated using V79-379A cells under aerobic and anaerobic conditions ($IC_{50} = 0.149 \pm 0.011$ and $0.0116 \pm 0.0008 \mu M$, respectively; hypoxic cytotoxicity ratio ($C_{50}[air] / C_{50}[N_2]$) = 12.8). It also showed selective cytotoxicity against non-small cell lung cancer H460 cells with high NAD(P)H dehydrogenase (quinone) (NAD[P]H:quinone oxidoreductase) activity ($IC_{50} = 0.018 \pm 0.004 \mu M$) over H596 cells with no enzyme activity ($IC_{50} = 9.22 \pm 1.51 \mu M$), giving a selectivity ratio of 510. Other related indolequinones include the following:



Compound	R1	R2	Formula
261136	H	H	C ₁₂ H ₁₂ N ₂ O ₂
261137	Me	CH ₂ OH	C ₁₄ H ₁₆ N ₂ O ₃

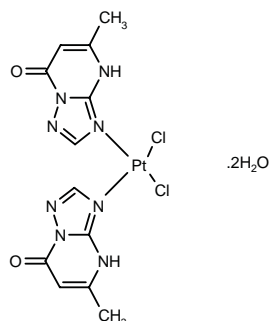
SOURCE – BTG.

REFERENCES

1. Stratford, I.J. et al. (British Technol. Group, Ltd.) Indolequinone derivs. as bioreductive agents. WO 9723456.
2. Beall, H.D. et al. Bioactivation of novel indolequinones, mitosenes and cyclopropamitosenes by NAD(P)H:quinone oxidoreductase (NQO1): Structure metabolism and structure-cytotoxicity studies. Proc Amer Assoc Cancer Res 1997, 38: Abst 4112.
3. Beall, H.D. et al. Indolequinone antitumor agents: Relationship between quinone structure and rate of metabolism by recombinant human NQO1. Bioorg Med Chem Lett 1998, 8(5): 545.
4. Cotterill, A.S. et al. Cyclopropamitosenes, novel bioreductive anticancer agents. Synthesis, electrochemistry, and biological activity of 7-substituted cyclopropamitosenes and related indolequinones. J Med Chem 1994, 37(22): 3834.
5. Naylor, M.A. et al. 2-Cyclopropylindolequinones and their analogues as bioreductively activated antitumor agents: Structure-activity in vitro and efficacy in vivo. J Med Chem 1997, 40(15): 2335.

260568

(*SP-4-2*)-Dichlorobis[5-methyl-[1,2,4]triazolo[1,5-*a*]-pyrimidin-7(4*H*)-one-κ*N*³]platinum dihydrate



C12-H12-Cl2-N8-O2-Pt.2H2O; Mol wt: 602.31

ACTION – Antineoplastic platinum complex, a cisplatin analog with moderate antitumor activity against human breast carcinoma MCF-7 cells (ID₅₀ = 33.4 μM, 48-h exposure), but high activity against human ovarian carcinoma A121 cells (ID₅₀ = 14.3 μM, 48-h exposure); it was less active than cisplatin but more active than carboplatin against the latter cell line.

SOURCES – Univ. Claude Bernard Lyon I, Villeurbanne (FR); Univ. Granada, Granada (ES); Univ. Sevilla, Sevilla (ES).

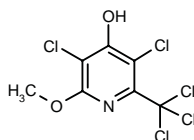
REFERENCES

1. Navarro, J.A.R. et al. *cis*-[PtCl₂(4,7-*H*-5-methyl-7-oxo[1,2,4]triazolo[1,5-*a*]pyrimidine)2]: A sterically restrictive new cisplatin analogue. Reaction kinetics with model nucleobases, DNA interaction studies, antitumor activity, and structure-activity relationships. *J Med Chem* 1998, 41(3): 332.

4-DEMETHYLPENCLOMEDINE**260063**

3,5-Dichloro-4-hydroxy-2-methoxy-6-(trichloromethyl)-pyridine

4-DM-PEN



C7-H4-Cl5-N-O2; Mol wt: 311.38

ACTION – The major human plasma metabolite of the chemotherapeutic agent penclomedine. Although it is inactive *in vitro* against tumor cells, it shows comparable activity to penclomedine against human mammary cancer MX-1, renal cancer CAKI-1 and colon cancer HT29 tumor xenografts in mice, and against a panel of human CNS tumor xenografts in nude mice. In contrast to penclomedine, it appears to be devoid of neurotoxicity and thus may be more suitable for clinical development.

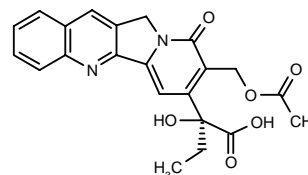
SOURCES – Johns Hopkins Univ., Baltimore, MD (US); Dept. Health Human Serv., Rockville, MD (US); Southern Res. Inst., Birmingham, AL (US).

REFERENCES

1. Hartman, N. et al. (Dept. Health Human Services [USA]; Southern Res. Inst.; Johns Hopkins Univ. School Med.) *Pyridine deriv., compsn. and method for treating cancer*. WO 9746531.
2. Friedman, H. et al. *Treatment of CNS tumor xenografts with penclomedine (PEN) and 4-demethylpenclomedine (4-DM-PEN)*. *Proc Amer Assoc Cancer Res* 1998, 39: Abst 1488.
3. Struck, R.F. et al. *Antitumor evaluation and proposed mechanism of action of 4-demethylpenclomedine (DM-PEN)*. *Proc Amer Assoc Cancer Res* 1998, 39: Abst 1489.
4. Waund, W.R. et al. *4-Demethylpenclomedine, an antitumor-active, potentially non-neurotoxic metabolite of penclomedine*. *Cancer Res* 1997, 57(5): 815.

ANTIBIOTICS AND ALKALOIDS**259001**

2(*S*)-[8-(Acetoxymethyl)-9-oxo-9,11-dihydroindolizino[1,2-*b*]quinolin-7-yl]-2-hydroxybutyric acid



C22-H20-N2-O6; Mol wt: 408.41

ACTION – Water-soluble antineoplastic and antiviral alkaloid isolated from *Mappia foetida* or produced from camptothecin. It was tested for *in vitro* cytotoxic activity against colon carcinoma HCT116 cells (IC₅₀ = 8.2 nM; IC₅₀ camptothecin = 10.5 nM) and resistant HCT116/VM46 cells (IC₅₀ = 25.3 nM; IC₅₀ camptothecin = 96.7 nM).

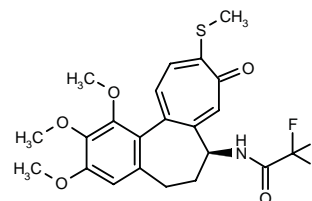
SOURCE – Indena.

REFERENCES

1. Bombardelli, E. and Verotta, L. (Indena SpA) *Camptothecin-skeleton cpds. isolated from Mappia foetida and the use thereof as syntones for novel medicaments as well as therapeutical agents*. WO 9743290.

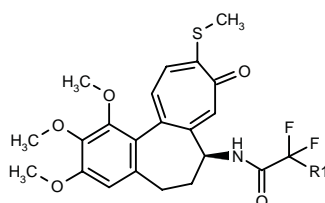
IDN-5005**260706**

2,2,2-Trifluoro-*N*-[1,2,3-trimethoxy-10-(methylsulfanyl)-9-oxobenzo[*a*]heptalen-7(*S*)-yl]acetamide



C22-H22-F3-N-O5-S; Mol wt: 469.47

ACTION – Antineoplastic agent, a colchicine analog that exhibits potent antiproliferative activity against human breast cancer MDA-MB-231 and MCF-7/ADR cell lines (IC_{50} = 1.3 and 35 nM, respectively, vs. 1.8 and 12,000 nM, respectively, for colchicine), as well as against the multidrug-resistant human leukemia cell line CEM-VBL (IC_{50} = 2 nM vs. 260 nM for colchicine). Title compound was also found to be effective against lymphocytic leukemia P388 in mice (minimum effective dose [MED; T/C >125] = 0.32 mg/kg i.p.). IDN-5005 was also more active than colchicine in its cell cycle-blocking and apoptosis-inducing effects. The LD_{50} in mice is 0.9 mg/kg i.p. Other fluorinated colchicine analogs reported to be more stable in solution are:



Compound	R1	Formula
IDN-5079* [248017]	CF3	C ₂₃ H ₂₂ F ₃ NO ₅ S
IDN-5080** [248019]	CF ₂ CF ₃	C ₂₄ H ₂₂ F ₇ NO ₅ S

SOURCE – Indena.

REFERENCES

- Bombardelli, E. and Gabetta, B. (Indena SpA) *Colchicine derivs., the use thereof and formulations containing them*. JP 97500883, WO 9701570.
- De Vincenzo, R. et al. *Antiproliferative activity of colchicine analogues on MDR-positive and MDR-negative human cancer cell lines*. Anti-Cancer Drug Design 1998, 13(1): 19.
- Kerekes, P. et al. *Synthesis and biological effects of novel thiocolchicines. 3. Evaluation of N-acyldeacetylthiocolchicines, N-(alkoxycarbonyl)deacetylthiocolchicines, and O-ethyldeacetylthiocolchicines. New synthesis of thiodemecolcine and antileukemic effects of 2-demethyl- and 3-demethylthiocolchicine*. J Med Chem 1985, 28(9): 1204.
- Quinn, F.R. and Beisler, J.A. *Quantitative structure-activity relationships of colchicines against P388 leukemia in mice*. J Med Chem 1981, 24(3): 251.
- Quinn, F.R. et al. *Toxicity quantitative structure-activity relationships of colchicines*. J Med Chem 1981, 24(5): 636.

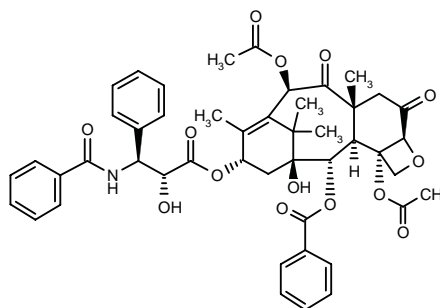
*Identified compound **248017** (see **247696**) Drug Data Rep 1997, 19(6): 561.

Identified compound **248019 (see **247696**) Drug Data Rep 1977, 19(6): 561.

ANTIMITOTIC DRUGS

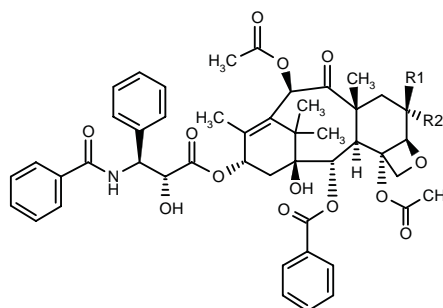
259913

[2a*R*-[2a α ,4a β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12a α ,12b α]]-6,12b-Diacetoxy-9-(3-benzamido-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz-[1,2-*b*]oxete-3,5-dione



C₄₇H₄₉N-O₁₄; Mol wt: 851.90

ACTION – Antineoplastic agent, a paclitaxel derivative shown to prolong survival time in mice bearing Madison 109 lung carcinoma following both i.p. (T/C x 100 = 128% at 100 mg/kg/day on days 5 and 8 postimplant) and i.v. administration (T/C x 100 = 133% at 15 mg/kg/day on days 4, 5, 6, 7 and 8 postimplant). Other compounds from this series of 7-deoxy-6-substituted paclitaxel derivatives include the following:



Compound	R1	R2	Formula
260679	H	OH	C ₄₇ H ₅₁ NO ₁₄
260680	OH	H	C ₄₇ H ₅₁ NO ₁₄
260681	OH	Me	C ₄₈ H ₅₃ NO ₁₄

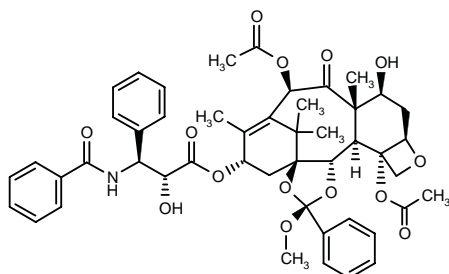
SOURCE – Bristol-Myers Squibb.

REFERENCES

- Wittman, M.D. et al. (Bristol-Myers Squibb Co.) *7-Deoxy-6-substd. paclitaxels*. WO 9746232.

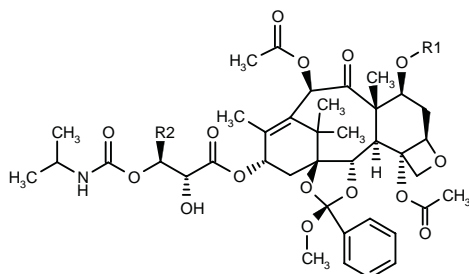
261161

[2*R*,3*aS*-(2 α ,5 β ,8 α ,9 α ,10 α ,11 α β ,13 α β ,13 β β ,13 α)]-8,13*a*-Diacetoxy-5-[3(*S*)-benzamido-2(*R*)-hydroxy-3-phenylpropionyloxy]-10-hydroxy-2-methoxy-6,9*a*,14,14-tetramethyl-2-phenyl-4,5,8,9,9*a*,10,11,11*a*,13,13*a*,13*b*,13*c*-dodecahydro-3*a*,7-methano-3*aH*-oxeto[2'',3''':5',6']benzo[1',2':3,4]cyclodeca[1,2-*d*]-[1,3]dioxol-9-one

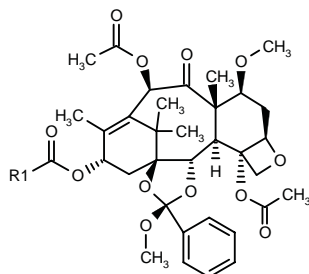


C48-H53-N-O14; Mol wt: 867.95

ACTION – Antineoplastic agent, a taxane derivative with potent cytotoxicity against human colon carcinoma HCT-116 cells (IC_{50} = 6.0 nM). *In vivo*, it prolonged the survival time of mice bearing M109 lung carcinoma when given at 100 mg/kg i.v. on days 5 and 8 postimplantation (T/C = 130%). Within this series of ortho-ester paclitaxel derivatives, the following are also included:



Compound	R1	R2	Formula
261429	H	Ph	C ₄₈ H ₅₅ NO ₁₅
261430	Me	2-furyl	C ₄₄ H ₅₅ NO ₁₆



Compound	R1	Formula
261431	(<i>E</i>)-2-furyl-CH=CH	C ₄₀ H ₄₆ O ₁₃
261432	(<i>R,R</i>)-2-furyl-CH(OH)CH(OH)	C ₄₀ H ₄₈ O ₁₅

SOURCE – Bristol-Myers Squibb.

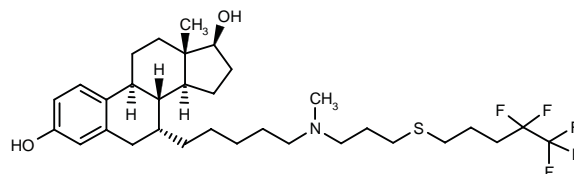
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HORMONAL AGENTS

259872

7 α -[5-[*N*-Methyl-*N*-[3-(4,4,5,5,5-pentafluoropentyl-sulfanyl)propyl]amino]pentyl]estra-1,3,5(10)-trien-3,17 β -diol



C32-H48-F5-N-O2-S; Mol wt: 605.79

ACTION – Antiestrogenic agent for the treatment of estrogen-dependent disorders such as breast or endometrial cancer, prostatic hyperplasia, anovular infertility and melanoma. *In vitro*, it exhibited antiproliferative activity against human cervical cancer HeLa cells (IC_{50} = 0.3 nM) and the human breast cancer MCF-7-derived cell line MVLN (IC_{50} = 1.0 nM). *In vivo*, it exhibited potent and dose-dependent antiuterotrophic effects in immature rats following s.c. or p.o. administration. Potent antiproliferative activity was demonstrated against mouse mammary MXT tumors at 10 mg/kg/day x 14 days, producing similar results to ovariectomy. It also showed antiproliferative activity against DMBA- and NMU-induced mammary tumors in rats, producing complete inhibition of tumor growth at 3 mg/kg/day p.o. x 4 weeks and 10 mg/kg/day p.o. x 4 weeks, respectively, being more potent in both tests than tamoxifen at 5 mg/kg.

SOURCE – Schering AG.

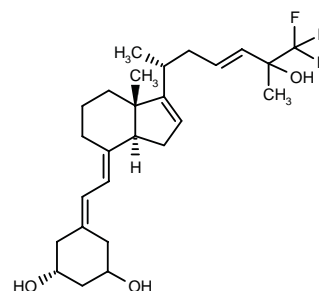
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1. Bittler, D. et al. (Schering AG) 7 α -(5-Methylaminopentyl)-estratrienes, process for the preparation thereof, pharmaceutical preparations which contain said 7 α -(5-methylaminopentyl)-estratrienes and use thereof for production of drugs. WO 9745441.

RO-25-9716

260504

(23*E*)-26,26,26-Trifluoro-1,25-dihydroxy-16,17,23,24-tetradecahydro-19-norvitamin D₃



C26-H37-F3-O3; Mol wt: 454.57

ACTION – Vitamin D₃ analog that potently inhibits the proliferation of human meyloid leukemia cell lines including poorly differentiated lines and also induces differentiation in such cell lines. For example, it inhibited the growth of HL-60 cells with an ED₅₀ of 0.04 nM and it induced the expression of CD11b in 92% of HL-60 cells at a concentration of 1 nM. Potentially useful in the treatment of myeloid leukemia and myelodysplastic syndromes.

SOURCE – Roche.

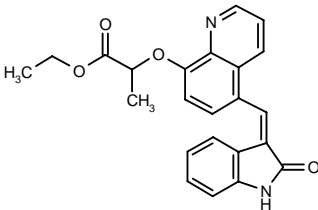
REFERENCES

1. Asou, H. et al. 19-Nor vitamin D₃ analogues: A new class of potent inhibitors of proliferation and inducers of differentiation of human myeloid leukemia cell lines. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 363.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

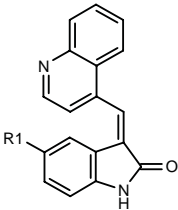
260068

2-[5-(2-Oxoindolin-3-ylidenemethyl)quinolin-8-yloxy]-propionic acid ethyl ester



C23-H20-N2-O4; Mol wt: 388.42

ACTION – Antineoplastic agent, a tyrosine kinase inhibitor (IC₅₀ = 15 μM against p45 v-abl kinase) with good water solubility (> 10 mg/ml); it inhibited the growth of human myeloid leukemia K562 cells with an IC₅₀ of 39.5 μM. Other specifically claimed compounds within this series of substituted quinolymethylen-oxindole derivatives include the following:



Compound	R1	Formula
261688	NHCH2CH2N(Me)2	C ₂₂ H ₂₂ N ₄ O
261689	4-morpholinyl-CH2CH2NH	C ₂₄ H ₂₄ N ₄ O ₂
261690	NHCH2CH2NHCOCH2NH2	C ₂₂ H ₂₁ N ₅ O ₂
261691	NHC(=NH)N(Me)2	C ₂₁ H ₁₉ N ₅ O
261692	N=CHN(Me)2	C ₂₁ H ₁₈ N ₄ O

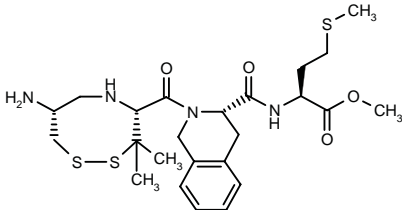
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Battistini, C. et al. (Pharmacia & Upjohn SpA) Substd. quinolymethylen-oxindole analogues as tyrosine kinase inhibitors. WO 9746551.

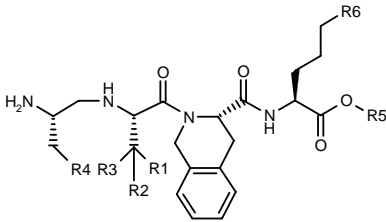
261159

N-[2-[7(R)-Amino-3,3-dimethyl-1,2-dithia-5-azacyclo-octan-4(R)-ylcarbonyl]-1,2,3,4-tetrahydroisoquinolin-3(S)-ylcarbonyl]-L-methionine methyl ester

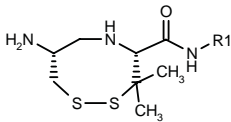


C24-H36-N4-O4-S3; Mol wt: 540.75

ACTION – Agent for the treatment of proliferative disorders such as cancer, restenosis, benign prostatic hyperplasia, atherosclerosis and fibrosis that acts by inhibiting prenyl transferases. Other specifically claimed compounds include the following:



Compound	R1=R2	R3	R4	R5	R6	Formula
261433	Me	SCH2NHAc	SH	Me	SMe	C ₂₇ H ₄₃ N ₅ O ₅ S ₃
261434	H	-S-S-		H	SMe	C ₂₁ H ₃₀ N ₄ O ₄ S ₃
261435	H	SCH2NHAc	SH	Me	SMe	C ₂₈ H ₃₉ N ₅ O ₅ S ₃
261438	H	-S-S-		Me	Me	C ₂₃ H ₃₄ N ₄ O ₄ S ₂



Compound	R1	Formula
261436	2,3-(Me)2-Ph	C ₁₈ H ₂₅ N ₃ OS ₂
261437	2,3-(Cl)2-PhCH2	C ₁₅ H ₂₁ Cl ₂ N ₃ OS ₂

SOURCE – Biomeasure.

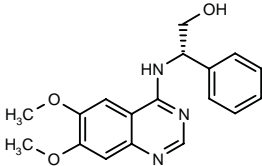
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1. Kim, S.H. (Biomeasure, Inc.) Prenyl transferase inhibitors. WO 9800411.

FCE-29771

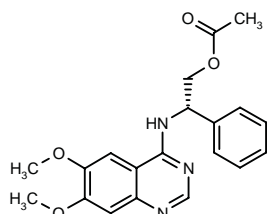
260184

2(S)-(6,7-Dimethoxyquinazolin-4-ylamino)-2-phenyl-ethanol



C18-H19-N3-O3; Mol wt: 325.37

ACTION – Antineoplastic agent, a tyrosine kinase inhibitor proven to inhibit epidermal growth factor (EGF) receptor autophosphorylation in human epithelial carcinoma A431 cell crude membrane extracts and in A431 cells with IC_{50} values of 0.024 and 0.8 μ M, respectively. When tested for antiproliferative activity against carcinoma A431 it exhibited an IC_{50} value > 1.56 μ M. Also useful for the treatment of psoriasis, restenosis, diabetic complications, for the control of angiogenesis and as an immuno-suppressant. Another specifically claimed compound from this series of bicyclic 4-aralkylaminopyrimidine derivatives is:



FCE-29772 [261447]: C20-H21-N3-O4

SOURCE – Pharmacia & Upjohn.

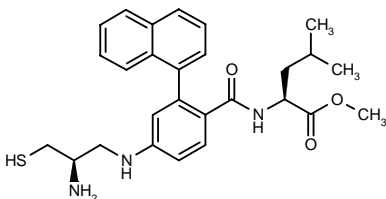
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1. Brasca, M.G. et al. (Pharmacia & Upjohn SpA) *Bicyclic 4-aralkylaminopyrimidine derivs. as tyrosine kinase inhibitors*. WO 9749689.

GGTI-298

261684

(*R*)-*N*-[4-(2-Amino-3-sulfanylpropylamino)-2-(1-naphthyl)benzoyl]-L-leucine methyl ester



C27-H33-N3-O3-S; Mol wt: 479.64

ACTION – Antineoplastic agent, a geranylgeranyl-transferase-I inhibitor that blocks tumor cells in the G0/G1 phase of the cell cycle, apparently by inducing accumulation of the cyclin-dependent kinase (CDK) inhibitor p21^{WAF} in a p53-independent manner. GGTI-298 inhibited tumor growth by 60% in nude mice bearing human lung Calu-1 and A-5A9 tumors.

SOURCES – Univ. Pittsburgh, Pittsburgh, PA (US); Univ. South Florida, Tampa, FL (US); Yale Univ., New Haven, CT (US).

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2. Sebt, S. and Hamilton, A. (Univ. Pittsburgh) *Inhibitors of prenyl transferases*. WO 9621456.
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4. Lerner, E.C. et al. *Inhibition of K-Ras but not H- or N-Ras prenylation requires both farnesyltransferase and geranylgeranyltransferase I inhibitors in human tumor cell lines*. Proc Amer Assoc Cancer Res 1997, 38: Abst 2357.

5. McGuire, T.F. et al. *Platelet-derived growth factor receptor tyrosine phosphorylation requires protein geranylgeranylation but not farnesylation*. J Biol Chem 1996, 271(44): 27402.

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7. Sun, J. et al. *GGTI-298 blocks human tumor growth in G0/G1 by a mechanism involving induction of p21WAF, Rb hypophosphorylation and inhibition of cyclin-dependent kinases*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1842.

8. Sun, J. et al. *Both farnesyltransferase and geranylgeranyltransferase I inhibitors are required for disruption of K-Ras prenylation but each alone is sufficient for inhibition of human tumor growth*. Proc Amer Assoc Cancer Res 1997, 38: Abst 2356.

9. Vogt, A. et al. *Inhibition of protein geranylgeranylation arrests human tumor cells in G1 through a p53 independent induction of p21WAF1/CIP1/SDI1*. Proc Amer Assoc Cancer Res 1997, 38: Abst 2358.

10. Vogt, A. et al. *The geranylgeranyltransferase-I inhibitor GGTI-298 arrests human tumor cells in G0/G1 and induces P21WAF1/CIP1/SDI1 in a p53-independent manner*. J Biol Chem 1997, 272(43): 27224.

NSC-330507

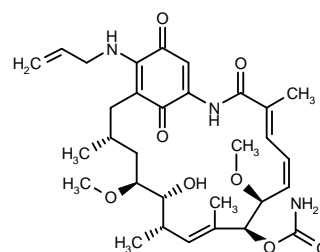
231090

(4*E*,6*Z*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-19-(Allylamino)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaene-3,20,22-trione

17-(Allylamino)-17-demethoxygeldanamycin

CP-127374

NSC-330507D



C31-H43-N3-O8; Mol wt: 585.70

ACTION – A geldanamycin prodrug that selectively inhibits the *erbB-2* oncoprotein p185. It depleted p185 contents in cultured human breast cancer SKBr-3 cells (IC_{50} = 24-31 nM), and it inhibited p185 phosphotyrosine (60 and 80% inhibition, respectively, at 100 and 200 mg/kg i.p.) and also significantly inhibited tumor growth at a dose of 50 mg/kg b.i.d. x 5 days in nude mice bearing s.c. FRE/*erbB-2* tumors..

SOURCE – Pfizer.

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1. Gallaschun, R.J. et al. (Pfizer, Inc.) *Ansamycin derivs. as antioncogene and anticancer agents*. EP 706516, JP 96506356, WO 9501342.
2. Egorin, M.J. et al. *Metabolism of 17-(allylamino)-17-demethoxygeldanamycin (17AAG) (NSC 330507) by murine and human hepatic preparations*. Proc Amer Assoc Cancer Res 1998, 39: Abst 3567.
3. Eiseman, J.L. et al. *Plasma pharmacokinetics and tissue distribution of 17-allylamino-17-demethoxygeldanamycin (NSC 330507), a prodrug for geldanamycin, in CD2F1 mice and Fisher 344 rats*. Proc Amer Assoc Cancer Res 1997, 38: Abst 2063.
4. Miller, P. et al. *Depletion of the *erbB-2* gene product p185 by benzoquinoid ansamycins*. Cancer Res 1994, 54(10): 2724.

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8. Schnur, R.C. et al. *Inhibition of the oncogene product p185erbB-2 in vitro and in vivo by geldanamycin and dihydrogeldanamycin derivatives*. J Med Chem 1995, 38(19): 3806.

9. Schnur, R.C. et al. *erbB-2 oncogene inhibition by geldanamycin derivatives: Synthesis, mechanism of action, and structure-activity relationships*. J Med Chem 1995, 38(19): 3813.

ANTIANGIOGENIC AGENTS

259054

Chimeric VEGF receptor protein

ACTION – Antiangiogenic protein comprising amino acid sequences from the vascular endothelial growth factor (VEGF) receptors flt-1 and KDR (or the murine homolog of the KDR receptor, FLK-1), for the treatment of undesired vascularization such as tumor formation. It binds to and inactivates VEGF, thereby reducing or inhibiting endothelial cell proliferation and angiogenesis.

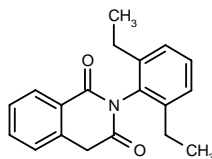
SOURCE – Genentech.

REFERENCES

1. Davis-Smyth, T.L. et al. (Genentech, Inc.) *Novel inhibitors of vascular endothelial growth factor activity, their uses and processes for their production*. WO 9744453.

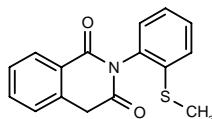
260570

2-(2,6-Diethylphenyl)isoquinolin-1,3(2H,4H)-dione



C19-H19-N-O2; Mol wt: 293.36

ACTION – Potent, specific, nonpeptide aminopeptidase N (microsomal aminopeptidase) inhibitor ($IC_{50} = 0.12 \mu\text{g/ml}$ using human acute lymphoblastic leukemia MOLT-4 cells; IC_{50} dipeptidyl peptidase IV $> 100 \mu\text{g/ml}$). A potential lead compound for the development of low-molecular-weight aminopeptidase N inhibitors for preventing metastasis. Another related compound with a similar profile is:



260569: C16-H13-N-O2-S

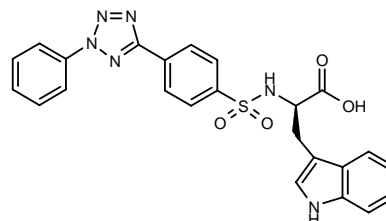
SOURCE – Ishihara Sangyo.

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1. Miyachi, H. et al. *Novel potent nonpeptide aminopeptidase N inhibitors with a cyclic imide skeleton*. J Med Chem 1998, 41(3): 263.

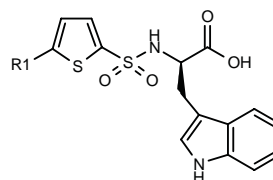
260690

N-[4-(2-Phenyl-2H-tetrazol-5-yl)phenylsulfonyl]-D-tryptophan

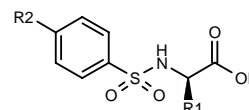


C24-H20-N6-O4-S, Mol wt: 488.52

ACTION – Orally active antineoplastic and antimetastatic agent, a potent and highly selective inhibitor of human matrix metalloproteinases (MMPs) such as gelatinase A (MMP-2; $IC_{50} = 0.019 \mu\text{M}$) and gelatinase B (MMP-9; $IC_{50} = 0.032 \mu\text{M}$), whereas no activity was detected against other metalloproteinases ($IC_{50} > 1.0 \mu\text{M}$). Title compound demonstrated oral activity in animal models of tumor growth and metastasis, inhibiting lung colonization in the Lewis lung carcinoma model in mice and increasing survival in mice bearing human lung cancer Ma44 cells. Other related compounds include the following:



Compound	R1	Formula
260691	4-Me-Ph	$C_{22}H_{20}N_2O_4S_2$
260693	4-Me-Ph-ethynylene	$C_{24}H_{20}N_2O_4S_2$



Compound	R1	R2	Formula
260692	i-Pr	4-MeS-Ph	$C_{18}H_{21}NO_4S_2$
260694	i-Pr	2-(4-MeS-Ph)-5-tetrazolyl	$C_{19}H_{21}N_5O_4S_2$
260695	3-indolyl-CH2	4-Br-PhCONH	$C_{24}H_{20}BrN_3O_5S$

SOURCE – Shionogi.

REFERENCES

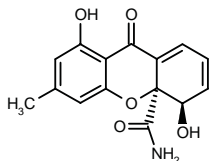
1. Watanabe, F. et al. (Shionogi & Co., Ltd.) *Sulfonated amino acid derivs. and metalloproteinase inhibitors containing the same*. WO 9727174.

2. Tamura, Y. et al. *Highly selective and orally active inhibitors of type IV collagenase (MMP-9 and MMP-2): N-Sulfonylamino acid derivatives*. J Med Chem 1998, 41(4): 640.

MISCELLANEOUS ANTINEOPLASTIC AGENTS

259195

(4*R*,4*aS*)-4,8-Dihydroxy-6-methyl-9-oxo-4,4*a*-dihydro-9*H*-xanthen-4*a*-carboxamide



C15-H13-N-O5; Mol wt: 287.27

ACTION – Antineoplastic agent, a derivative of F-390 with improved *in vivo* antitumor activity. *In vitro* cytotoxicity was tested against murine leukemia P388, human leukemia K562 and human colon carcinoma HCT-116 (IC₅₀ = 0.015, 0.17 and 0.096 µg/ml, respectively). *In vivo*, it protected mice bearing colon 26 tumors from mortality up to day 17, producing 42% inhibition of tumor growth when given at 10 mg/kg i.v. on days 7, 11 and 15 following tumor implantation.

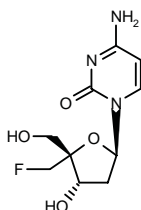
SOURCE – Ajinomoto.

REFERENCES

1. Sato, S. et al. (Ajinomoto Co., Ltd.) *Novel xanthone derivs.* JP 97316069.

259209

2'-Deoxy-4'-(fluoromethyl)cytidine



C10-H4-F-N3-O4; Mol wt: 249.16

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against human leukemia CCRF-HSB-2 cells, giving an IC₅₀ value in the range 0.077-0.082 µg/ml.

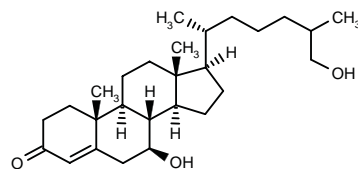
SOURCE – Yamasa Shoyu.

REFERENCES

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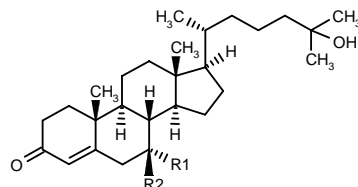
259871

7β,26-Dihydroxy-4-cholesten-3-one



C27-H44-O3; Mol wt: 416.64

ACTION – Cytostatic sterol for the treatment of cancers such as melanoma, breast carcinoma and colon carcinoma, as well as psoriasis. The proliferation of virus-transformed human fibroblasts was selectively inhibited by the compound compared to normal human fibroblasts (cell viability = 11% vs. 122% at 1.25 µM, 72 h); it also reduced the viability of human colon carcinoma cells and malignant melanoma cells (cell viability = 24 and 26%, respectively, at 2.5 µM, 48 h). Other specifically claimed cholesterol derivatives include the following:



Compound	R1	R2	Formula
261381	OH	H	C ₂₇ H ₄₄ O ₃
261382	H	OH	C ₂₇ H ₄₄ O ₃

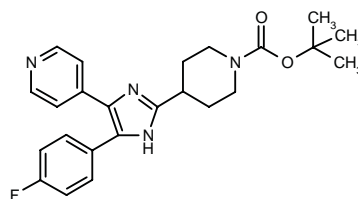
SOURCE – Medivir.

REFERENCES

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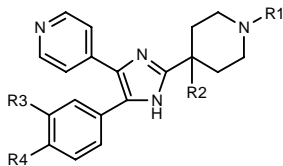
260056

4-[5-(4-Fluorophenyl)-4-(4-pyridyl)-1*H*-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester

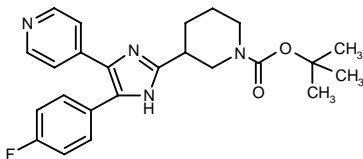


C24-H27-F-N4-O2; Mol wt: 422.50

ACTION – Agent for the treatment of cancer, inflammation, osteoporosis, bone resorption and Crohn's disease that acts by inhibiting Raf kinase activity and the production or activity of cytokines such as IL-1, IL-6, IL-8 and TNF (tumor necrosis factor). Within this series of specifically claimed substituted imidazoles, the following are also included:



Compound	R1	R2	R3	R4	Formula
260228	t-BuOCO	CH2Ph	H	F	C ₃₁ H ₃₃ FN ₄ O ₂
260230	Ac	H	H	F	C ₂₁ H ₂₁ FN ₄ O
260231	H	H	H	F	C ₁₉ H ₁₉ FN ₄
260232	H	H	Cl	Cl	C ₁₉ H ₁₈ Cl ₂ N ₄
260233	Me	H	Cl	Cl	C ₂₀ H ₂₀ Cl ₂ N ₄
260234	1,3-dioxo-2-isindolinylnyl-(CH2)4	H	Cl	Cl	C ₃₁ H ₂₉ Cl ₂ N ₅ O ₂
260235	1,3-dioxo-2-isindolinylnyl-(CH2)6	H	Cl	Cl	C ₃₃ H ₃₃ Cl ₂ N ₅ O ₂
260236	CH2Ph	H	Cl	Cl	C ₂₆ H ₂₄ Cl ₂ N ₄
260237	4-Pyr-CH2CH2	H	Cl	Cl	C ₂₆ H ₂₅ Cl ₂ N ₅



260229: C24-H27-F-N4-O2

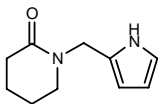
SOURCE – Merck & Co.

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1. Selnick, H.G. et al. (Merck & Co., Inc.) *Substd. imidazoles having anti-cancer and cytokine inhibitory activity*. US 5717100.

260069

1-(1*H*-Pyrrol-2-ylmethyl)piperidin-2-one



C10-H14-N2-O; Mol wt: 178.23

ACTION – Antimetastatic agent that acts by inhibiting cell migration due to overexpression of UNC-53, as shown *in vitro* in murine neuroblastoma N4 cells transfected with the *unc-53* gene.

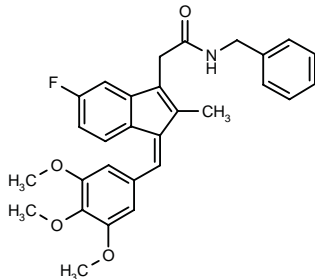
SOURCE – Janssen.

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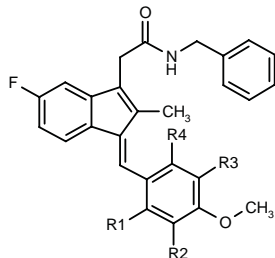
260093

N-Benzyl-2-[5-fluoro-2-methyl-1 (*Z*)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide



C29-H28-F-N-O4; Mol wt: 473.54

ACTION – Agent for the treatment of precancerous lesions and neoplasms, particularly colonic polyps, an analog of sulindac with potent tumor cell growth-inhibitory activity, as demonstrated against human colon carcinoma SW-480 cells (IC₅₀ = 0.04 μM), and apoptosis-inducing properties, as measured using human colon carcinoma HT-29 cells (73% apoptotic cells at 1 μM; EC₅₀ for DNA fragmentation = 0.05 μM). Compound proved to be a weak cyclooxygenase type 1 (COX-1) inhibitor (< 25% inhibition at 100 μM using purified enzyme from sheep seminal vesicles) and is thus expected to be devoid of the side effects of sulindac and other NSAIDs. Other specifically claimed substituted benzylidene indenyl formamides, acetamides and propionamides include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
260711	OMe	H	H	OMe	Z	C ₂₉ H ₂₈ FNO ₄
260712	H	OMe	OMe	H	E	C ₂₉ H ₂₈ FNO ₄
260713	H	H	OMe	OMe	Z	C ₂₉ H ₂₈ FNO ₄
260714	H	OMe	H	OMe	Z	C ₂₉ H ₂₈ FNO ₄

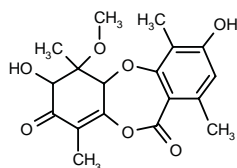
SOURCES – Univ. Arizona, Tucson, AZ (US); Cell Pathways.

REFERENCES

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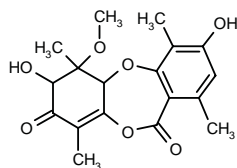
260108

(+)-3,7-Dihydroxy-6-methoxy-1,4,6,9-tetramethyl-5a,6,7,8-tetrahydro-11*H*-dibenzo[*b,e*][1,4]dioxepine-8,11-dione (isomer a)



C18-H20-O7; Mol wt: 348.35

ACTION – Antineoplastic agent produced by culturing a microorganism belonging to the genus *Aspergillus* (e.g., *Aspergillus fumigatus* NR7329 or *Aspergillus japonicus* NR-7328). Antiproliferative activity was demonstrated against the colorectal carcinoma cell lines HT-29 (IC₅₀ = 5.8 μM), SW480 (IC₅₀ = 3-10 μM) and HCT116 (IC₅₀ = 1.3 μM), as well as against the lung carcinoma cell line H460A (IC₅₀ = 2.3 μM), the breast carcinoma cell line MCF-7 (IC₅₀ = 1.5 μM) and the osteosarcoma cell line SAOS-2 (IC₅₀ = 0.3-1 μM). Another related compound is:



260792: C18-H20-O7: (–)-isomer

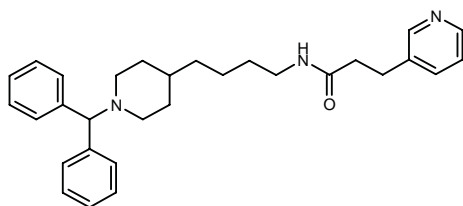
SOURCE – Roche.

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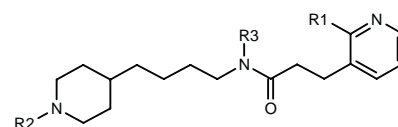
260129

N-[4-[1-(Diphenylmethyl)piperidin-4-yl]butyl]-3-(3-pyridyl)propionamide

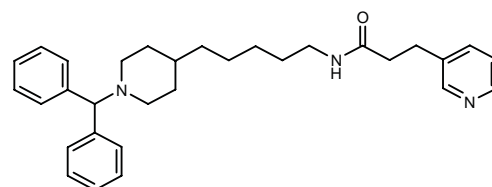


C30-H37-N3-O; Mol wt: 455.64

ACTION – Antineoplastic agent and immunosuppressant shown to potently inhibit the proliferation of several human tumor cell lines including colon cancer HT-29, hepatocellular carcinoma HepG2, estrogen receptor-positive breast carcinoma MCF-7, osteosarcoma Saos-2, monocytic leukemia THP-1 and Burkitt's lymphoma Namalwa cells (IC₅₀ = 0.08, 0.02, 0.08, 0.02, 0.03 and 0.05 μM, respectively). Immunosuppressive activity was demonstrated by strong inhibition of mouse spleen lymphocyte proliferation (IC₅₀ = 0.003 μM). A representative compound from a series of pyridyl alkane acid amides, wherein the following are also specifically claimed:



Compound	R1	R2	R3	Formula
260981	H	Ac	H	C ₁₉ H ₂₉ N ₃ O ₂
260982	H	CH ₂ Ph	H	C ₂₄ H ₃₃ N ₃ O
260983	H	1-Naph-NHCO	H	C ₂₈ H ₃₄ N ₄ O ₂
260984	F	CH(Ph) ₂	H	C ₃₀ H ₃₆ FN ₃ O
260985	H	CH(Ph) ₂	OH	C ₃₀ H ₃₇ N ₃ O ₂



260986: C31-H39-N3-O

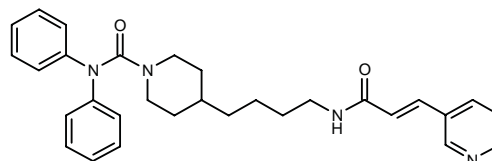
SOURCE – Klinge Pharma.

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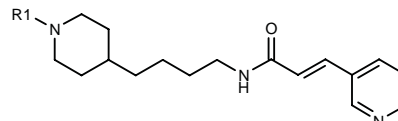
260130

N-[4-[1-(*N,N*-Diphenylcarbamoyl)piperidin-4-yl]butyl]-3-(3-pyridyl)-2-propenamide

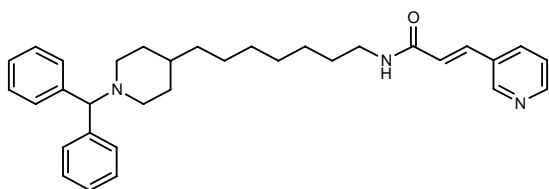
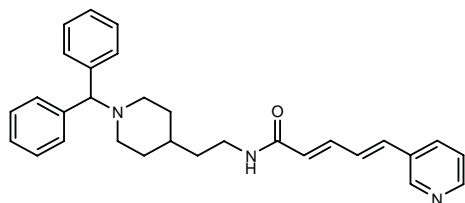


C30-H34-N4-O2; Mol wt: 482.62

ACTION – Antineoplastic agent and immunosuppressant whose antiproliferative activity was tested against human hepatocellular carcinoma HepG2 cells (IC₅₀ = 0.001 μM). It exhibited potent immunosuppressive activity when assayed for inhibition of mouse spleen lymphocyte proliferation (IC₅₀ = 0.04 nM). Other specifically claimed compounds from this series of pyridyl alkene- and pyridyl alkane acid amides include the following:



Compound	R1	Formula
260987	SO ₂ Me	C ₁₈ H ₂₇ N ₃ O ₃ S
260988	Ac	C ₁₉ H ₂₇ N ₃ O ₂
260989	3-Pyr-CH(Ph)	C ₂₉ H ₃₄ N ₄ O
260991	COPh	C ₂₄ H ₂₉ N ₃ O ₂

**260990:** C33-H41-N3-O**260992:** C30-H33-N3-O

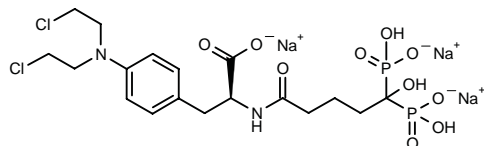
SOURCE – Klinge Pharma.

REFERENCES

1. Biedermann, E. et al. (Klinge Pharma GmbH) *Pyridyl alkene- and pyridyl alkine- acid amides as cytostatics and immunosuppressives*. WO 9748696.

260201

4-[Bis(2-chloroethyl)amino]-*N*-(5-hydroxy-5,5-diphosphonopentany)-L-phenylalanine trisodium salt



C18-H25-Cl2-N2-Na3-O10-P2; Mol wt: 631.23

ACTION – Bisphosphonate with dual antitumor and bone resorption-inhibitory activity, particularly useful for the treatment of bone tumors. Compound was tested *in vivo* in rats bearing intratibially implanted mammary carcinoma Walker 256/8 and was found to significantly inhibit tumor growth (84% tumor weight inhibition) and to completely protect against bone lesions at 30 mg/kg i.v. administered on days 1, 4 and 7 after tumor implantation. Compound is also reported to be effective in a model of human multiple myeloma in SCID mice, and to possess low toxicity and high water solubility.

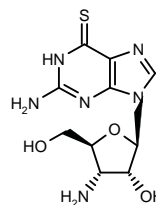
SOURCE – Boehringer Mannheim.

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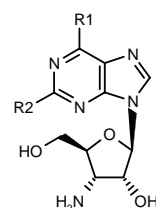
260526

3'-Amino-3'-deoxy-6-thioguanosine



C10-H14-N6-O3-S; Mol wt: 298.32

ACTION – Antineoplastic agent with *in vitro* cytotoxicity against human leukemia K562 ($IC_{50} = 0.19 \mu\text{g/ml}$). A representative compound from a series of 3'-amino-3'-deoxyribonucleosides, wherein the following are also included:



Compound	R1	R2	Formula
261485	Me	H	C ₁₁ H ₁₅ N ₅ O ₃
261486	SMe	H	C ₁₁ H ₁₅ N ₅ O ₃ S
261487	NHEt	H	C ₁₂ H ₁₈ N ₆ O ₃
261488	NHPr	H	C ₁₃ H ₂₀ N ₆ O ₃
261489	i-PrNH	H	C ₁₃ H ₂₀ N ₆ O ₃
261490	SH	H	C ₁₀ H ₁₃ N ₅ O ₃ S
261491	NH2	NH2	C ₁₀ H ₁₅ N ₇ O ₃

SOURCE – Toagosei.

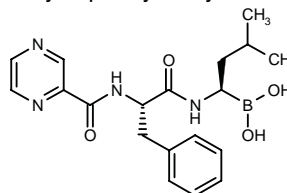
REFERENCES

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260757

[3-Methyl-1(*R*)-(2-pyrazinylcarbonyl-L-phenyl-alanyl-amino)butyl]boronic acid

Pyrazin-2-ylcarbonyl-L-phenylalanyl-L-boroleucine



C19-H25-B-N4-O4; Mol wt: 384.24

ACTION — Potent and selective proteasome inhibitor from a series of dipeptidyl boronic acids, showing subnanomolar potency against the enzyme ($K_i = 0.62 \text{ nM}$) and high selectivity relative to other serine proteases ($K_i > 300 \text{ nM}$). It is reported to be active in animal models indicative of antitumor and antiinflammatory activity and is suggested to represent a promising new therapy for cancer and inflammatory disorders.

The 20S proteasome is known to play an essential physiological role in intracellular protein turnover in eukaryotic cells, but it has also been implicated in inappropriate or accelerated protein degradation associated with pathological conditions such as cancer, where unregulated proteasome-mediated degradation of cell cycle-regulatory proteins and tumor suppressor genes results in accelerated and uncontrolled mitosis.

SOURCE – ProScript.

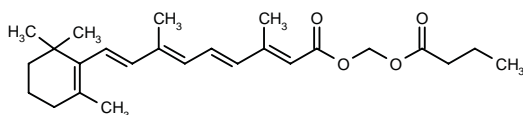
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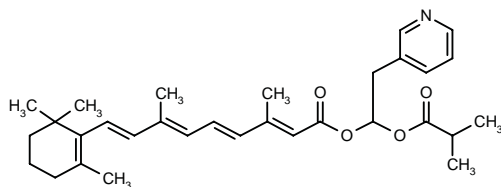
261141

(all *E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoic acid butyryloxymethyl ester



C25-H36-O4; Mol wt: 400.56

ACTION – Antiproliferative and differentiation-inducing agent, a retinoyloxy(substituted) alkylene butyrate that is more potent than retinoic acid or butyric acid, or combination of the two. *In vitro*, it potently induced differentiation of human promyelocytic leukemia HL-60 cells (81% at 1.0 μ M), being clearly more potent than butyric acid alone (BA; 6% at 1.0 μ M), retinoic acid alone (RA; 21% at 1.0 μ M) or a combination of BA plus RA (29% at 50 μ M BA + 0.5 μ M RA). Another specifically claimed compound is:



261596: C31-H41-N-O4

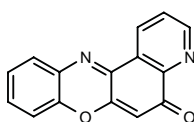
SOURCE – Bar Ilan Univ., Ramat-Gan (IL).

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261509

5*H*-Pyrido[3,2-*a*]phenoxazin-5-one



C15-H8-N2-O2; Mol wt: 248.24

ACTION – Antiproliferative agent that inhibits the proliferation of a variety of tumor cell lines including cells resistant to etoposide, camptothecin, vincristine and hydroxyurea, with 1000-fold less toxicity against nonproliferating cells; it reduced KB cell clonogenicity by 90% after 24 h of exposure at a concentration of 30 nM. It was found to inhibit DNA synthesis at 30 nM and both DNA and RNA synthesis at 300 nM. The compound appears to act on a new cellular target involved in the S-phase of the cell cycle.

SOURCES – Univ. di Cagliari, Cagliari (IT); Univ. Federico II, Naples (IT); Yale Univ., New Haven, CT (US).

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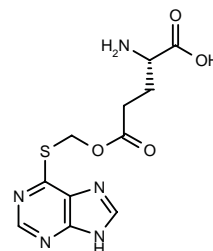
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6-MPG

233450

L-Glutamic acid 5-(9*H*-purin-6-ylsulfanylmethyl)monoester



C11-H13-N5-O4-S; Mol wt: 311.31

ACTION – Antineoplastic agent, a water-soluble 6-mercaptapurine derivative that combines a direct antitumor effect with the ability to enhance antitumor immunity and appears to be less toxic than the parent compound at equimolar doses. The compound exhibited complete inhibition of the growth of colon 26 tumors in mice at the maximum tolerated dose of 200 mg/kg/day p.o. on days 1-7, with a higher therapeutic ratio (MTD/ED₅₀) than 6-mercaptapurine (> 8 vs. 6.3). It was highly effective in inhibiting secondary tumor growth (82.2% at 50 mg/kg/day i.p. on days 3-7; 87.1% at 100 mg/kg/day i.p. on days 3-7) in a double-grafted Meth A fibrosarcoma tumor system in mice, and also inhibited primary tumor growth (56.7% at 100 mg/kg/day i.p. on days 3-7); significant secondary tumor growth inhibition (58.4%) was also observed in mice in whom the primary tumor was excised prior to administration of 6-MPG, and 11/20 of these animals remained tumor-free compared to only 2/16 of those in whom primary tumor was not excised. Cancer therapy with 6-MPG would thus appear to be especially beneficial after surgical removal of primary tumors.

SOURCE – Tanabe Seiyaku.

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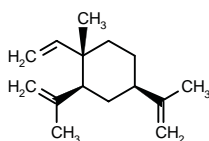
ELEMENE

257947

(1 α ,2 β ,4 β)-2,4-Diisopropenyl-1-methyl-1-vinylcyclohexane

(1 α ,2 β ,4 β)-1-Ethenyl-1-methyl-2,4-bis(1-methylethenyl)-cyclohexane

β -Elemene



C15-H24; Mol wt: 204.35

ACTION – Naturally occurring antineoplastic agent isolated from the traditional Chinese medicinal herb *Rhizoma Zedoariae*, whose activity appears to involve both direct cytotoxic effects and an indirect immunostimulating effect. Elemene selectively inhibits the growth of a wide range of tumor cell lines compared to normal peripheral blood leukocytes, and its cytotoxic effect appears to involve inhibition of mitosis, induction of apoptosis and an antioxidant action. Results from clinical trials indicate excellent tolerance with no bone marrow suppression, and high efficacy in patients with malignant pleural or peritoneal effusions, primary hepatocarcinoma, lung cancer, brain cancer and superficial cancers.

SOURCE – Dalian Jin Gang.

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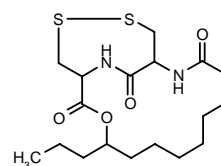
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MONOGRAPH – Wang, X.-W. *Elemene*. Drugs Fut 1998, 23(3): 266.

FE-399

259056

11-Propyl-12-oxa-16,17-dithia-2,20-diazabicyclo-[12.4.2]icosane-3,13,19-trione



C18-H30-N2-O4-S2; Mol wt: 402.57

ACTION – Antineoplastic agent obtained from a culture of the filamentous fungus *Ascochyta* sp. AJ117309 (FERM BP-5517), shown to inhibit tumor growth in mice bearing colon 26 carcinoma by 61% on day 15 postimplantation when given at a dose of 8 mg/kg i.p. x 4 days (63% inhibition for cisplatin at 5 mg/kg i.p. x 3 days).

SOURCE – Ajinomoto.

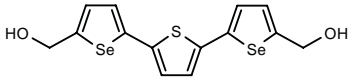
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NSC-676632

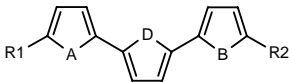
259909

1,1'-(Thiophene-2,5-diyl)bis(selenophene-2,5-diyl)bis-(methanol)



C14-H12-O2-S-Se2; Mol wt: 402.23

ACTION – Antineoplastic agent with enhanced cytotoxicity against human renal carcinoma A-498 cells (GI_{50} = 0.3 μ g/ml) relative to normal human renal cells (GI_{50} = 2000 μ g/ml) giving a selective cytotoxicity index of over 1000. It also exhibited activity against other human tumor cell lines in the NCI panel, particularly ovarian and other renal cancer cell lines, and it inhibited protein kinase C (PKC) with an IC_{50} of 50 μ g/ml. Within this series of selenophene compounds, the following are also included:



Compound	R1	R2	A=B	D	Formula
NSC-675246 [260730]	H	CH2OH	Se	Se	C ₁₃ H ₁₀ OSe ₃
NSC-675247 [260731]	CH2OH	CH2OH	Se	Se	C ₁₄ H ₁₂ O ₂ Se ₃
NSC-675344 [260732]	H	CH2OH	S	Se	C ₁₃ H ₁₀ OS ₂ Se
NSC-676634 [260733]	H	CHO	Se	NH	C ₁₃ H ₉ NOSe ₂
NSC-676635 [260734]	H	CH2OH	Se	NH	C ₁₃ H ₁₁ NOSe ₂

SOURCE – Purdue Res. Found., West Lafayette, IN (US).

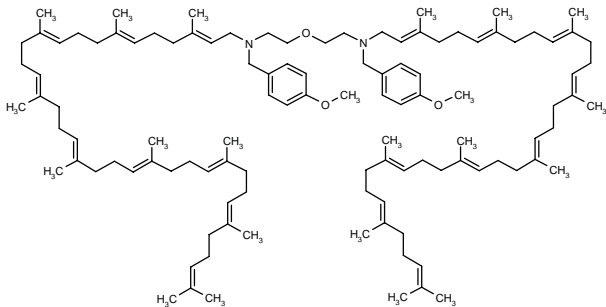
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RESISTANCE MODIFIERS

257480

(all *E*)-*N,N'*-Oxybis(ethylene)bis[*N*-(4-methoxybenzyl)-*N*-(3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaenyl)amine]



C110-H172-N2-O3; Mol wt: 1570.58

ACTION – Antineoplastic enhancer that potentiates the carcinostatic activity of doxorubicin against human mammary carcinoma MCF-7/WT cells, the IC_{50} value for doxorubicin being 14.5 ng/ml in the absence of test compound and 8 ng/ml when doxorubicin was combined with 50 μ M of test compound. A representative compound within a series of aminoethyl ether derivatives.

SOURCE – Nisshin Flour Milling.

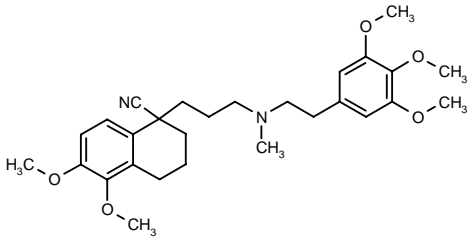
REFERENCES

1. Inomata, K. et al. (Nisshin Flour Milling Co., Ltd.) *Amino ethyl ether derivs*. JP 97268165.

KR-30035

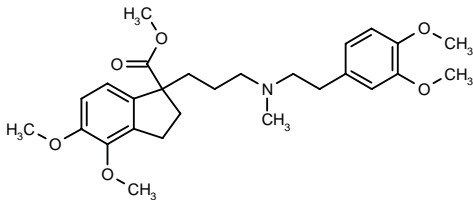
261014

5,6-Dimethoxy-1-[3-[*N*-methyl-*N*-[2-(3,4,5-trimethoxyphenyl)ethyl]amino]propyl]-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



C28-H38-N2-O5; Mol wt: 482.62

ACTION – Modulator of multidrug resistance (MDR), a verapamil analog with activity at least comparable to verapamil in enhancing paclitaxel and doxorubicin cytotoxicity but significantly reduced cardiovascular effects. KR-30035 potentiated paclitaxel- and doxorubicin-induced cytotoxicity in P-glycoprotein-expressing human HCT15 cells and multidrug-resistant HCT15/CL02 cells, and it enhanced rhodamine accumulation in these cell lines; in contrast, it showed no such effect in non-P-glycoprotein-expressing SK-OV-3 cells. The compound was much less potent than verapamil in relaxing norepinephrine-precontracted rat aorta (EC_{50} = 6.40 μ M vs. 0.32 μ M) and in reducing left ventricular pressure in isolated guinea pig hearts (EC_{50} = 14.1 μ M vs. 12 μ M). Another related compound is:



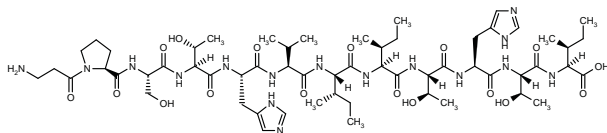
KR-30032 [261013]: C27-H37-N-O6

SOURCE – Korea Res. Inst. Chem. Technol., Taejon (KR).

REFERENCES

1. Choi, S.U. et al. *Reversal of multidrug resistance by novel verapamil analogs in cancer cells*. Anti-Cancer Drugs 1998, 9(2): 157.

ACTION – Agent for the treatment or prevention of infections such as bacterial, fungal, viral or protozoal infections, particularly in immunosuppressed patients, that possesses neutrophil- and monocyte/macrophage-stimulating activity. Another related peptide is:



260906: C58-H96-N16-O17

SOURCE – Peptech.

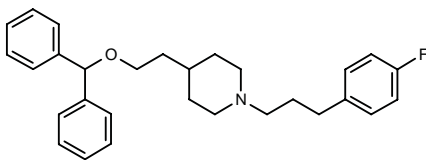
REFERENCES

1. Rathjen, D.A. et al. (Peptech, Ltd.) *Novel peptides for prevention and treatment of infection*. WO 9748725.

TREATMENT OF POISONING AND DRUG DEPENDENCY

261314

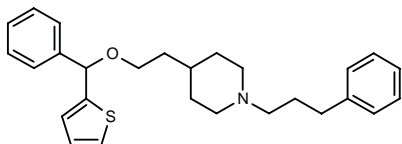
4-[2-(Benzylhydroxy)ethyl]-1-[3-(4-fluorophenyl)propyl]piperidine



C29-H34-F-N-O; Mol wt: 431.59

Oxalate salt, m.p. 164.9-5.8 °C.

ACTION – Potent and selective dopamine transporter ligand (IC_{50} = 6.6 nM for displacement of [3H]-Win-35428 binding in rat striatum) with much lower affinity for the serotonin transporter (IC_{50} = 223.4 nM for displacement of [3H]-citalopram binding in rat striatum), potentially useful as a cocaine antagonist. Another related 4-[2-(diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine analog is:



261315: C27-H33-N-O-S

SOURCES – Univ. Illinois, Peoria, IL (US); Organix.

REFERENCES

1. Dutta, A.K. et al. *Potent and selective ligands for the dopamine transporter (DAT): Structure-activity relationship studies of novel 4-[2-(diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine analogues*. J Med Chem 1998, 41(5): 699.

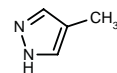
FOMEPIZOLE⁺

Rec INN; USAN

168144

4-Methylpyrazole

4-MP



C4-H6-N2; Mol wt: 82.10

M.p. 15.5-5.8 °C.

ACTION – Competitive inhibitor of alcohol dehydrogenase, the enzyme that catalyzes the oxidation of ethanol to acetaldehyde and the initial steps of ethylene glycol and methanol metabolism to their toxic metabolites.

INDICATION – Antidote for ethylene glycol (antifreeze) poisoning or for use in suspected ethylene glycol ingestion.

PRESENTATION – Vials for i.v. injection (1.5 ml), 1 g/ml.

PROPRIETARY NAME – Antizol (US).

SOURCE – Orphan Medical.

REFERENCES

1. Chen, W.J.A. et al. *4-Methylpyrazole, an alcohol dehydrogenase inhibitor, exacerbates alcohol-induced microencephaly during the brain growth spurt*. Alcohol 1995, 12(4): 351.
2. Dang Vu, B. et al. *Analytical and kinetic study of 4-methylpyrazole, a new antidote for the treatment of ethylene glycol poisoning summary*. Ann Fals Exp Chim 1992, 85(906): 99.
3. Davis, G.J. et al. *Determinants of 4-methylpyrazole affinity in class I (beta) alcohol dehydrogenases*. FASEB J 1994, 8(7): Abst 502.
4. Dial, S.M. *4-Methylpyrazole as an antidote for ethylene glycol intoxication in dogs and cats*. Diss Abst Int 1990, 50(8): 3348-B.
5. Grauer, G.F. et al. *Comparison of the effects of ethanol and 4-methylpyrazole on the pharmacokinetics and toxicity of ethylene glycol in the dog*. Toxicol Lett 1987, 35(2-3): 307.
6. Iaquinto, G. et al. *4-Methylpyrazole-induced increases in adherent gastric mucus secretion in rats*. Gastroenterology 1995, 108(4, Suppl.): A119.
7. Likforman, J. et al. *4-Methylpyrazole. Monograph*. J Toxicol Clin Exp 1987, 7(6): 373.
8. Parodi, M.C. and Iaquinto, G. *4-Methylpyrazole (4-MP) prevents ethanol induced gastric mucosal damage in humans: Possible role of endogenous prostaglandin E2 (PGE2) and leukotriene C4 (LTC4)*. 9th Int Conf Prostaglandin Relat Compound (June 6-10, Florence) 1994, 125.
9. *Antizol cleared by FDA as first antidote for ethylene glycol poisoning*. Prous Science Daily Essentials December 19, 1997.
10. *Fomepizole launch*. Orphan Medical Company Communication 1998, February 11.
11. *Orphan Medical announces exclusive sublicense to develop 4-methyl pyrazole*. Orphan Medical Press Release 1993, December 22.
12. *Orphan Medical announces third quarter and year-to-date results*. Orphan Medical, Inc. Press Release 1996, October 30.
13. *Orphan Medical licenses out European rights to Antizol*. Prous Science Daily Essentials September 23, 1997.
14. *Orphan Medical submits NDA for Antizol™ (fomepizole) for injection*. Orphan Medical, Inc. Press Release 1996, December 6.
15. *Product development status*. Orphan Medical Company Communication 1998, February 11.
16. *Proposed international nonproprietary names (Prop. INN): List 63*. WHO Drug Inform 1990, 4(2): 85.

17. Chronimed Inc. Form 10-K for the fiscal year ended July 1, 1994.

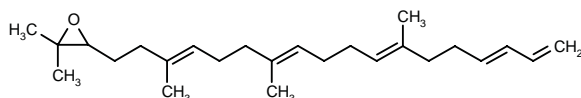
18. Orphan Medical Annual Report 1995.

*Drug Data Rep 1994, 16(6): 594.

PHARMACOLOGICAL TOOLS

260686

(all *E*)-2,2-Dimethyl-3-(3,7,12-trimethyl-3,7,11,15,17-octadecapentaenyl)oxirane



C25-H40-O; Mol wt: 356.59

Colorless oil.

ACTION – Potent and irreversible lanosterol synthase inhibitor, as shown using partially purified enzymes from pig liver and *Saccharomyces cerevisiae* microsomes (IC_{50} = 3.5 and 1.5 μ M, respectively). Potentially useful as a tool for assessing the mechanism of squalene 2,3-epoxide cyclization, and in the design of more specific hypocholesterolemic and antifungal drugs.

SOURCE – Univ. Torino., Torino (IT).

REFERENCES

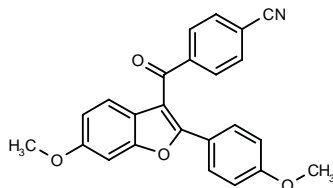
1. Ceruti, M. et al. 29-Methylidene-2,3-oxidosqualene derivatives as stereospecific mechanism-based inhibitors of liver and yeast oxidosqualene cyclase. *J Med Chem* 1998, 41(4): 540.

LY-320135*

235102

4-[6-Methoxy-2-(4-methoxyphenyl)benzofuran-3-yl-carbonyl]benzonitrile

[6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]furan-3-yl](4-cyanophenyl)methanone



C24-H17-N-O4; Mol wt: 383.40

ACTION – Selective brain cannabinoid CB_1 receptor antagonist with over 70-fold selectivity relative to the peripheral CB_2 receptor, as demonstrated in binding studies using receptors stably expressed in cell lines (K_i = 224 nM vs. > 10 μ M), as well as rat cerebellum (K_i = 203 nM) and rat spleen membrane preparations (K_i > 10 μ M). The compound antagonized the anandamide-induced inhibition of forskolin-stimulated cAMP accumulation in

CB_1 receptor-expressing CHO cells, and it blocked Win-55212-2-mediated inhibition of N-type calcium currents in N18 cells (IC_{50} = 55 ± 10 nM) and the activation of inward rectifying K^+ channels in AtT-20 cells. LY-320135 is thus a promising lead compound for the development of potent and selective cannabinoid antagonists for use in the characterization of cannabinoid receptor subtypes.

SOURCE – Lilly.

REFERENCES

1. Fahey, K.J. et al. (Eli Lilly & Co.) *Cannabinoid receptor antagonists*. EP 766559, JP 98503185, WO 9602248, US 5596106.

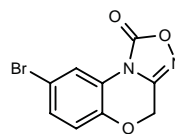
2. Felder, C.C. et al. LY320135, a novel cannabinoid CB_1 receptor antagonist, unmasks coupling of the CB_1 receptor to stimulation of cAMP accumulation. *J Pharmacol Exp Ther* 1998, 284(1): 291.

*Identified compound 235102 Drug Data Rep 1996, 18(6): 506.

NS-2028

259661

8-Bromo-4*H*-1,2,4-oxadiazolo[3,4-*c*][1,4]benzoxacin-1-one



C9-H5-Br-N2-O3; Mol wt: 269.05

ACTION – Potent and specific inhibitor of soluble guanylyl cyclase (IC_{50} = 30 and 200 nM, respectively, for basal and SIN-1-stimulated enzyme activity in bovine lung; IC_{50} = 17 nM for *S*-nitroso-glutathione (GSNO)-enhanced enzyme activity in mouse cerebellum). The compound inhibited nitric oxide synthase (NOS)-dependent cGMP formation (IC_{50} = 19 and 60 nM, respectively, in mouse cerebellar slices and cultured cerebellar granule cells; IC_{50} = 30 nM in human umbilical vein endothelial cells). In addition, NS-2028 inhibited NO-dependent cellular responses in a number of biological systems including vascular and airways smooth muscle, endothelial cells and cerebellum. The compound was reported to be active in models of dermal inflammation. NS-2028 may be useful for assessing the role of soluble guanylyl cyclase in biological responses.

SOURCE – NeuroSearch.

REFERENCES

1. Olesen, S.-P. et al. Characterization of NS 2028 as a specific inhibitor of soluble guanylyl cyclase. *Brit J Pharmacol* 1998, 123(2): 299.

2. NeuroSearch Annual Report 1993.

17. Chronimed Inc. Form 10-K for the fiscal year ended July 1, 1994.

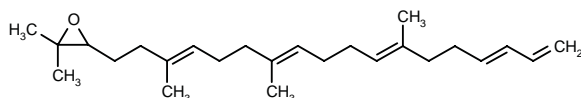
18. Orphan Medical Annual Report 1995.

*Drug Data Rep 1994, 16(6): 594.

PHARMACOLOGICAL TOOLS

260686

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SOURCE – Univ. Torino., Torino (IT).

REFERENCES

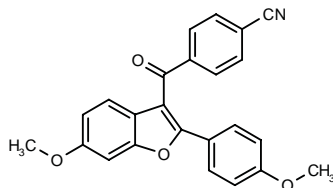
1. Ceruti, M. et al. 29-Methylidene-2,3-oxidosqualene derivatives as stereospecific mechanism-based inhibitors of liver and yeast oxidosqualene cyclase. *J Med Chem* 1998, 41(4): 540.

LY-320135*

235102

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CB_1 receptor-expressing CHO cells, and it blocked Win-55212-2-mediated inhibition of N-type calcium currents in N18 cells (IC_{50} = 55 ± 10 nM) and the activation of inward rectifying K^+ channels in AtT-20 cells. LY-320135 is thus a promising lead compound for the development of potent and selective cannabinoid antagonists for use in the characterization of cannabinoid receptor subtypes.

SOURCE – Lilly.

REFERENCES

1. Fahey, K.J. et al. (Eli Lilly & Co.) *Cannabinoid receptor antagonists*. EP 766559, JP 98503185, WO 9602248, US 5596106.

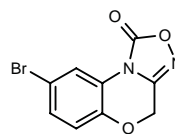
2. Felder, C.C. et al. LY320135, a novel cannabinoid CB_1 receptor antagonist, unmasks coupling of the CB_1 receptor to stimulation of cAMP accumulation. *J Pharmacol Exp Ther* 1998, 284(1): 291.

*Identified compound 235102 Drug Data Rep 1996, 18(6): 506.

NS-2028

259661

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C9-H5-Br-N2-O3; Mol wt: 269.05

ACTION – Potent and specific inhibitor of soluble guanylyl cyclase (IC_{50} = 30 and 200 nM, respectively, for basal and SIN-1-stimulated enzyme activity in bovine lung; IC_{50} = 17 nM for *S*-nitroso-glutathione (GSNO)-enhanced enzyme activity in mouse cerebellum). The compound inhibited nitric oxide synthase (NOS)-dependent cGMP formation (IC_{50} = 19 and 60 nM, respectively, in mouse cerebellar slices and cultured cerebellar granule cells; IC_{50} = 30 nM in human umbilical vein endothelial cells). In addition, NS-2028 inhibited NO-dependent cellular responses in a number of biological systems including vascular and airways smooth muscle, endothelial cells and cerebellum. The compound was reported to be active in models of dermal inflammation. NS-2028 may be useful for assessing the role of soluble guanylyl cyclase in biological responses.

SOURCE – NeuroSearch.

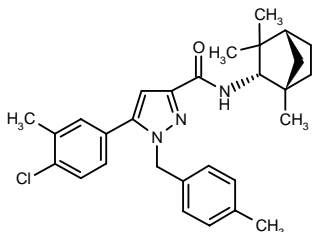
REFERENCES

1. Olesen, S.-P. et al. *Characterization of NS 2028 as a specific inhibitor of soluble guanylyl cyclase*. *Brit J Pharmacol* 1998, 123(2): 299.

2. NeuroSearch Annual Report 1993.

SR-144528***253448**

(1*S-endo*)-5-(4-Chloro-3-methylphenyl)-1-(4-methylbenzyl)-*N*-(1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)pyrazole-3-carboxamide



C29-H34-Cl-N3-O; Mol wt: 476.06

ACTION – Highly potent, selective and orally active cannabinoid CB₂ receptor antagonist with subnanomolar affinity for both rat spleen and cloned human CB₂ receptors (K_i = 0.3-0.6 nM), low affinity for rat brain and human CB₁ receptors (K_i = 305-437 nM) and no affinity for a number of other receptors, enzymes and channels. SR-144528 antagonized the CP-55940-induced inhibition of forskolin-stimulated adenylyl cyclase activity in human CB₂ receptor-expressing cell lines (EC_{50} = 10 nM) but not

in human CB₁ receptor-expressing cell lines, and it also selectively inhibited CP-55940-induced mitogen-activated protein kinase (MAP kinase) in human CB₂ receptor-expressing cells (IC_{50} = 39 nM vs. > 1 μ M in CB₁-expressing cells). Orally administered compound completely displaced [³H]-CP-55940 binding to mouse spleen membranes (ED_{50} = 0.36 mg/kg), with significant occupancy of the receptor for a least 18 h after a dose of 3 mg/kg p.o., whereas no effect on the binding to brain sites was observed at doses of up to 10 mg/kg p.o. or 10 μ g i.c.v. Potentially useful as a tool for investigating the *in vivo* functions of the cannabinoid system.

SOURCE – Sanofi.

REFERENCES

1. Barth, F. et al. (Sanofi) 3-Pyrazolecarboxamide derivs. having cannabinoid receptor affinity. FR 2742148, WO 9721682.
2. Bourri, B. et al. Lack of effect of cannabinoid receptor CB₂, agonist and antagonist on histamine release from human nasal polyp cells and blood leukocytes. J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 875.
3. Rinaldi-Carmona, M. et al. SR 144528, the first potent and selective antagonist of the CB₂ cannabinoid receptor. J Pharmacol Exp Ther 1998, 284(2): 644.

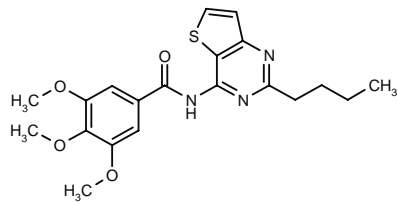
*Identified compound **253448** Drug Data Rep 1997, 19(10): 934.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

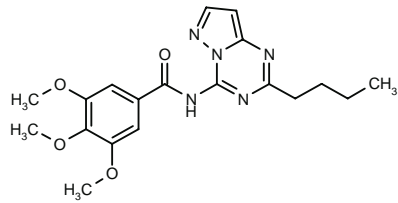
260073

N-(2-Butylthieno[3,2-d]pyrimidin-4-yl)-3,4,5-trimethoxybenzamide



C20-H23-N3-O4-S; Mol wt: 401.48

ACTION – Analgesic, antiinflammatory, antimicrobial, hypoglycemic, hypolipidemic, hypotensive and carcinostatic agent proven active against pressure-induced pain in rats at 10 mg/kg p.o. Another related compound is:



262227: C19-H23-N5-O4

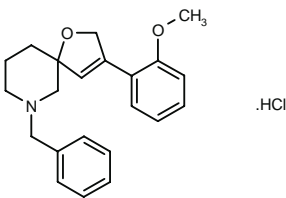
SOURCE – Otsuka.

REFERENCES

1. Okamura, T. et al. (Otsuka Pharm. Fac., Inc.) *Amide derivs.* WO 9746560.

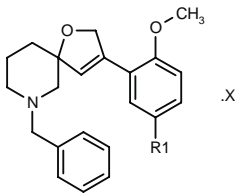
261211

7-Benzyl-3-(2-methoxyphenyl)-1-oxa-7-azaspiro[4.5]dec-3-ene hydrochloride



C22-H25-N-O2.HCl; Mol wt: 371.91

ACTION – Agent for the treatment of pain, inflammation, migraine, emesis and postherpetic neuralgia, a potent tachykinin, especially substance P (NK₁ receptor), antagonist. Within this series of specifically claimed spiro-piperidine derivatives, the following are also included:



Compound	R1	X	Formula
263015	5-CF3-1-tetrazolyl	HCl	C ₂₄ H ₂₄ F ₃ N ₅ O ₂ .HCl
263016	1-tetrazolyl	HCl	C ₂₃ H ₂₅ N ₅ O ₂ .HCl
263017	4-Pyr	2HCl	C ₂₇ H ₂₈ N ₂ O ₂ .2HCl
263018	CN	oxalate	C ₂₃ H ₂₄ N ₂ O ₂ .C ₂ H ₂ O ₄
263019	OCF3	HCl	C ₂₃ H ₂₄ F ₃ NO ₃ .HCl
263020	3-CF3-1,2,4-triazol-4-yl	HCl	C ₂₅ H ₂₅ F ₃ N ₄ O ₂ .HCl
263021	2-CF3-1-imidazolyl	HCl	C ₂₆ H ₂₆ F ₃ N ₃ O ₂ .HCl
263022	OCH2Ph		C ₂₉ H ₃₁ NO ₃

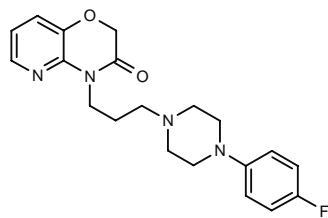
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Curtis, N.R. et al. (Merck Sharp & Dohme, Ltd.) *Spiro-piperidine derivs. and their use as therapeutic agents.* WO 9801450.

261302

4-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-3-one



C20-H23-F-N4-O2; Mol wt: 370.43

M.p. 103-4 °C.

ACTION – Nonopioid analgesic agent proven orally effective in the phenylquinone writhing test in mice (ED₅₀ = 12.5 mg/kg p.o.) and in the acetic acid writhing test in rats (ED₅₀ = 27.8 mg/kg p.o.), being more potent than acetylsalicylic acid (aspirin; ED₅₀ = 63 and 32 mg/kg p.o., respectively). Title compound was also active in the hot-plate test in mice, increasing the foot-licking latency at a dose of 32 mg/kg p.o. In mice, it induced sedation and hypothermia only at doses of 64 mg/kg p.o. and above, and the mortality threshold dose was found to be higher than 1024 mg/kg p.o. It exhibits some affinity for histamine H₁ and H₂ receptors, 5-HT_{1A} and 5-HT₂ receptors, and α₁- and α₂-adrenoceptors, whereas it is devoid of significant affinity for opioid receptors.

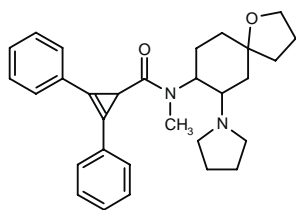
SOURCE – Servier.

REFERENCES

1. Savelon, L. et al. *Substituted pyrido[3,2-b]oxazin-3(4H)-ones: Synthesis and evaluation of antinociceptive activity.* Bioorg Med Chem 1998, 6(2): 133.

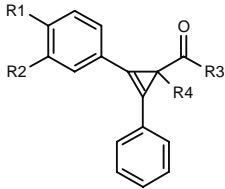
261537

N-Methyl-2,3-diphenyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]decan-8-yl]-2-cyclopropene-1-carboxamide



C30-H36-N2-O2; Mol wt: 456.63

ACTION – κ-Opioid receptor agonist, as demonstrated in the rabbit vas deferens assay (EC₅₀ = 12 nM), claimed for use in the treatment of pain, stroke, Parkinson's disease, dystonia, inflammation, cerebral ischemia, diuresis, asthma, psoriasis and irritable bowel syndrome. Other specifically claimed compounds from this series of diphenylcyclopropenes include the following:



Compound	R1	R2	R3	R4	Formula
262253	H	H	2-(1-pyrrolidinyl)-cyclohexyl-N(Me)	H	C ₂₇ H ₃₂ N ₂ O
262254	H	Cl	OEt	H	C ₁₈ H ₁₅ ClO ₂
262255	H	Cl	OH	H	C ₁₆ H ₁₁ ClO ₂
262256	H	Cl	2-(1-pyrrolidinyl)-cyclohexyl-N(Me)	H	C ₂₇ H ₃₁ ClN ₂ O
262257	Cl	H	OEt	H	C ₁₈ H ₁₅ ClO ₂
262258	Cl	H	OH	H	C ₁₆ H ₁₁ ClO ₂
262259	Cl	H	2-(1-pyrrolidinyl)-cyclohexyl-N(Me)	H	C ₂₇ H ₃₁ ClN ₂ O
262260	H	H	2-(1-pyrrolidinyl)-cyclohexyl-N(Me)	CO ₂ Me	C ₂₉ H ₃₄ N ₂ O ₃
262261	H	H	2-(1-pyrrolidinyl)-cyclohexyl-N(Me)	CO ₂ H	C ₂₈ H ₃₂ N ₂ O ₃

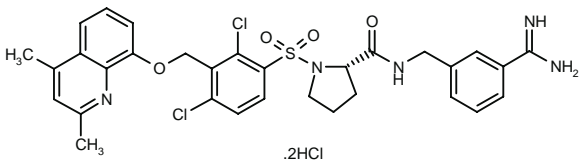
SOURCE – Warner-Lambert.

REFERENCES

1. Horwell, D.C. and Sabin, V. (Warner-Lambert Co.) *Diphenyl-cyclopropenes as selective κ-agonists.* WO 9803491.

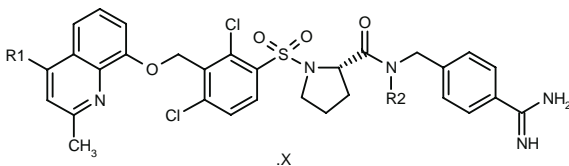
261542

N-(3-Amidinobenzyl)-1-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)phenylsulfonyl]pyrrolidine-2(S)-carboxamide dihydrochloride

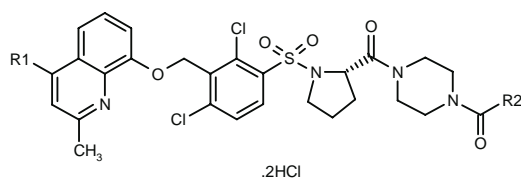


C31-H31-Cl2-N5-O4-S.2HCl; Mol wt: 713.50

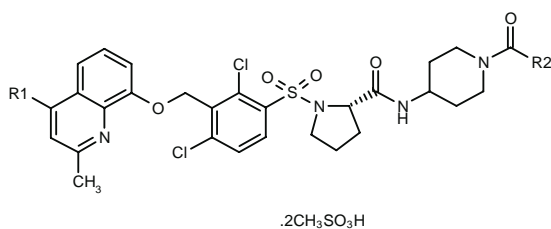
ACTION – Agent for the treatment of pain and inflammatory conditions including asthma, allergic rhinitis and traumatic brain injury that acts by virtue of its bradykinin B₂-antagonist activity (100% inhibition of [³H]-bradykinin binding in guinea pig ileum preparations at a concentration of 1 μM). Within this series of N-benzenesulfonyl-L-proline derivatives, the following are also included:



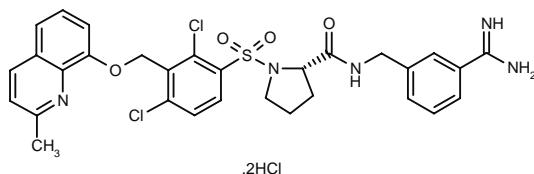
Compound	R1	R2	X	Formula
262156	Me	Me	2HCl	C ₃₂ H ₃₃ Cl ₂ N ₅ O ₄ S.2HCl
262157	Me	H	2CH ₃ SO ₃ H	C ₃₁ H ₃₁ Cl ₂ N ₅ O ₄ S.2CH ₄ O ₃ S
262158	H	H	2HCl	C ₃₀ H ₂₉ Cl ₂ N ₅ O ₄ S.2HCl



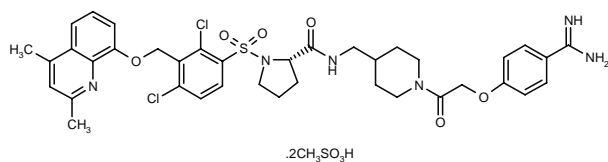
Compound	R1	R2	Formula
262160	Me	4-[NH ₂ C(=NH)]-Ph	C ₃₅ H ₃₆ Cl ₂ N ₆ O ₅ S.2HCl
262161	Me	4-[C(=NH)NH ₂]-PhCH ₂	C ₃₆ H ₃₆ Cl ₂ N ₆ O ₅ S.2HCl
262162	Me	4-[NH ₂ C(=NH)]-PhOCH ₂	C ₃₆ H ₃₆ Cl ₂ N ₆ O ₆ S.2HCl
262163	H	4-[NH ₂ C(=NH)]-Ph	C ₃₄ H ₃₄ Cl ₂ N ₆ O ₅ S.2HCl
262164	H	4-[C(=NH)NH ₂]-PhCH ₂	C ₃₅ H ₃₆ Cl ₂ N ₆ O ₅ S.2HCl
262165	H	4-[NH ₂ C(=NH)]-PhOCH ₂	C ₃₅ H ₃₆ Cl ₂ N ₆ O ₆ S.2HCl



Compound	R1	R2	Formula
262166	H	4-[NH ₂ C(=NH)]-Ph	C ₃₅ H ₃₆ Cl ₂ N ₆ O ₅ S.2CH ₄ O ₃ S
262167	Me	4-[NH ₂ C(=NH)]-Ph	C ₃₆ H ₃₆ Cl ₂ N ₆ O ₅ S.2CH ₄ O ₃ S
262168	Me	4-[NH ₂ C(=NH)]-PhOCH ₂	C ₃₇ H ₄₀ Cl ₂ N ₆ O ₆ S.2CH ₄ O ₃ S



262159: C30-H29-Cl2-N5-O4-S.2HCl



262169: C38-H42-Cl2-N6-O6-S.2CH4-O3-S

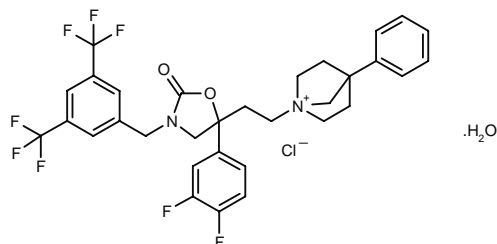
SOURCE – Fournier.

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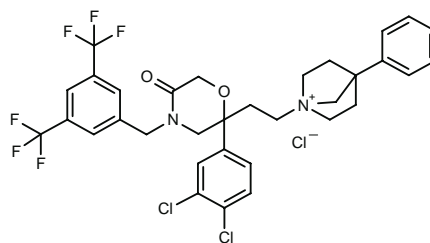
261588

(+)-1-[2-[3-[3,5-Bis(trifluoromethyl)benzyl]-5-(3,4-difluorophenyl)-2-oxooxazolidin-5-yl]ethyl]-4-phenyl-1-azoniabicyclo[2.2.1]heptane chloride hydrate



C32-H29-Cl-F8-N2-O2.H₂O; Mol wt: 679.05

ACTION – Tachykinin receptor antagonist with potential in the treatment of pain and inflammation, as well as immunological, gastrointestinal, cardiovascular and CNS disorders. Another compound from this series of 1-azoniabicyclo[2.2.1]heptane derivatives is:



262602: C33-H31-Cl3-F6-N2-O2

SOURCE – Sanofi.

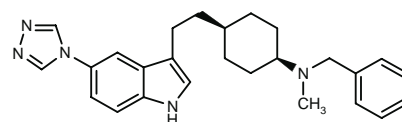
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ANTIMIGRAINE DRUGS

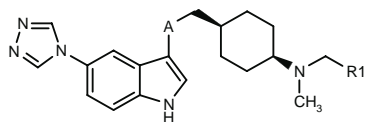
261543

cis-N-Benzyl-N-methyl-N-[4-[2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl]cyclohexyl]amine



C26-H31-N5; Mol wt: 413.56

ACTION – Antimigraine agent, a potent human 5-HT_{1Dα} (5-HT_{1D}) receptor agonist with at least 10-fold selectivity relative to the 5-HT_{1Dβ} (5-HT_{1B}) subtype, and thus expected to be associated with fewer side effects, notably cardiovascular effects, compared to non-subtype-selective compounds. Other specifically claimed compounds within this series of aminocyclohexane derivatives include the following:



Compound	R1	A	Formula
262170	Ph	-(CH ₂) ₂ -	C ₂₇ H ₃₃ N ₅
262171	CH ₂ Ph	-CH ₂ -	C ₂₇ H ₃₃ N ₅
262172	3-F-Ph	-CH ₂ -	C ₂₆ H ₃₀ FN ₅
262173	2-Pyr	-CH ₂ -	C ₂₅ H ₃₀ N ₆
262174	CH(Me)Ph	-CH ₂ -	C ₂₈ H ₃₅ N ₅
262175	CH(Me)Ph	-(CH ₂) ₂ -	C ₂₉ H ₃₇ N ₅
262176	4-F-Ph-CH(Me)	-CH ₂ -	C ₂₈ H ₃₄ FN ₅

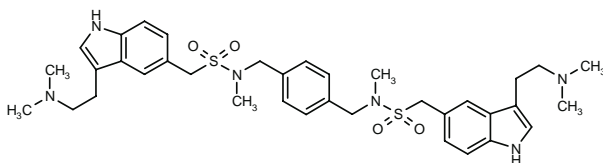
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Mcleod, A.M. et al. (Merck Sharp & Dohme, Ltd.) *Aminocyclohexane derivs. as 5-HT receptor agonists*. WO 9803504.

262247

N,N'-*p*-Xylene- α,α' -diylbis[3-[2-(dimethylamino)ethyl]-*N*-methyl-1*H*-indol-5-ylmethylsulfonamide]



C36-H48-N6-O4-S2; Mol wt: 692.93

ACTION – Antimigraine agent, a sumatriptan dimer that acts as a potent 5-HT_{1B} (K_i = 0.64 nM) and 5-HT_{1D} (K_i = 0.89 nM) receptor agonist with selectivity over 5-HT_{1A} receptors (K_i = 17.7 nM). Compound had an EC₅₀ of 0.58 nM for inhibition of forskolin-stimulated cAMP formation in CHO cells stably transfected with human 5-HT_{1B} receptors. It displayed a pD₂ value of 6.6 in the rabbit saphenous vein contraction model. The compound induced hypothermia in guinea pigs with an ED₅₀ of 1.3 mg/kg after i.p. administration, suggesting that it crosses the blood–brain barrier; it was also active after oral administration.

SOURCE – Pierre Fabre.

REFERENCES

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2. Perez, M. et al. *Dimerization of sumatriptan as an efficient way to design a potent, centrally and orally active 5-HT_{1B} agonist*. Bioorg Med Chem Lett 1998, 8: 675.

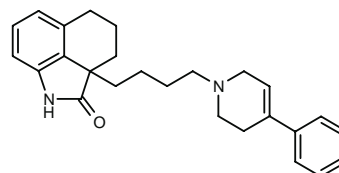
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

DR-4004

262291

2a-[4-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-2-one



C26-H30-N2-O; Mol wt: 386.54

ACTION – Potent human 5-HT₇ receptor antagonist (K_i = 2.1 nM) with selectivity over 5-HT₂ receptors (K_i = 92 nM). Potentially useful for the treatment of CNS disorders such as sleep disorders, anxiety and depression.

SOURCE – Meiji Seika.

REFERENCES

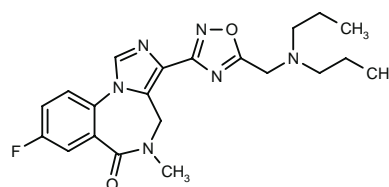
1. Koyama, M. et al. (Meiji Seika Co., Ltd.) *Tetrahydrobenzindole cpds*. WO 9800400.

2. Koyama, M. et al. *Tetrahydrobenzindoles, selective antagonists of the serotonin 5-HT₇ receptors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 149.

RO-48-6791

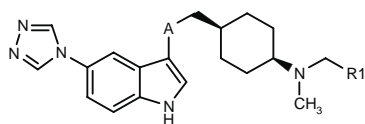
239170

3-[5-(Dipropylaminomethyl)-1,2,4-oxadiazol-3-yl]-8-fluoro-5-methyl-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one



C21-H25-F-N6-O2; Mol wt: 412.47

ACTION – Water-soluble full agonist at the benzodiazepine receptor shown to be slightly more potent and shorter acting than midazolam in animal models indicative of sedative effects. In an initial study in healthy volunteers, compound administered at doses of 0.1-3 mg i.v. as a 20-min infusion was found to be well tolerated and to elicit dose-dependent CNS depressant effects; it exhibited a comparable onset and duration of action to midazolam, but was 4-6-fold more potent and possessed a larger volume of distribution and plasma clearance. In subsequent studies in young and elderly volunteers, it was found to be about 2.5-fold more potent than midazolam in



Compound	R1	A	Formula
262170	Ph	-(CH ₂) ₂ -	C ₂₇ H ₃₃ N ₅
262171	CH ₂ Ph	-CH ₂ -	C ₂₇ H ₃₃ N ₅
262172	3-F-Ph	-CH ₂ -	C ₂₆ H ₃₀ FN ₅
262173	2-Pyr	-CH ₂ -	C ₂₅ H ₃₀ N ₆
262174	CH(Me)Ph	-CH ₂ -	C ₂₈ H ₃₅ N ₅
262175	CH(Me)Ph	-(CH ₂) ₂ -	C ₂₉ H ₃₇ N ₅
262176	4-F-Ph-CH(Me)	-CH ₂ -	C ₂₈ H ₃₄ FN ₅

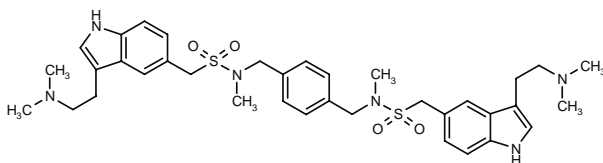
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Mcleod, A.M. et al. (Merck Sharp & Dohme, Ltd.) *Aminocyclohexane derivs. as 5-HT receptor agonists*. WO 9803504.

262247

N,N'-*p*-Xylene- α,α' -diylbis[3-[2-(dimethylamino)ethyl]-*N*-methyl-1*H*-indol-5-ylmethylsulfonamide]



C36-H48-N6-O4-S2; Mol wt: 692.93

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SOURCE – Pierre Fabre.

REFERENCES

1. Halazy, S. et al. (Pierre Fabre Medicament) *Novel sulphonamide bi-tryptamine derivs., method for preparing same, and use of said derivs. as drugs*. FR 2731224, WO 9626922.

2. Perez, M. et al. *Dimerization of sumatriptan as an efficient way to design a potent, centrally and orally active 5-HT_{1B} agonist*. Bioorg Med Chem Lett 1998, 8: 675.

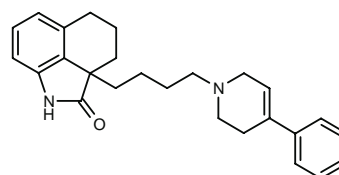
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

DR-4004

262291

2a-[4-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)butyl]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-2-one



C26-H30-N2-O; Mol wt: 386.54

ACTION – Potent human 5-HT₇ receptor antagonist (K_i = 2.1 nM) with selectivity over 5-HT₂ receptors (K_i = 92 nM). Potentially useful for the treatment of CNS disorders such as sleep disorders, anxiety and depression.

SOURCE – Meiji Seika.

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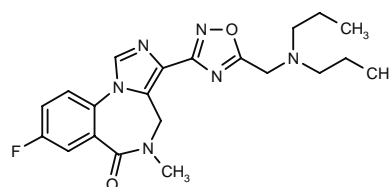
1. Koyama, M. et al. (Meiji Seika Co., Ltd.) *Tetrahydrobenzindole cpds*. WO 9800400.

2. Koyama, M. et al. *Tetrahydrobenzindoles, selective antagonists of the serotonin 5-HT₇ receptors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MED1 149.

RO-48-6791

239170

3-[5-(Dipropylaminomethyl)-1,2,4-oxadiazol-3-yl]-8-fluoro-5-methyl-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one



C21-H25-F-N6-O2; Mol wt: 412.47

ACTION – Water-soluble full agonist at the benzodiazepine receptor shown to be slightly more potent and shorter acting than midazolam in animal models indicative of sedative effects. In an initial study in healthy volunteers, compound administered at doses of 0.1-3 mg i.v. as a 20-min infusion was found to be well tolerated and to elicit dose-dependent CNS depressant effects; it exhibited a comparable onset and duration of action to midazolam, but was 4-6-fold more potent and possessed a larger volume of distribution and plasma clearance. In subsequent studies in young and elderly volunteers, it was found to be about 2.5-fold more potent than midazolam in

all volunteers and to exhibit reduced recovery periods. In a randomized, single-blind study in outpatients undergoing gastrointestinal endoscopic procedures, it was found to be more potent than midazolam, with a shorter duration of action and a better recovery profile. However, compound failed to demonstrate any advantage over midazolam in terms of onset or recovery in a double-blind, dose-ranging study in outpatients undergoing superficial surgical procedures.

SOURCE – Roche.

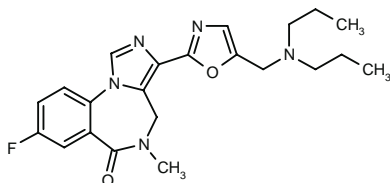
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3. Dingemanse, J. et al. *Integrated pharmacokinetics and pharmacodynamics of Ro 48-6791, a new benzodiazepine, in comparison with midazolam during first administration to healthy male subjects*. Brit J Clin Pharmacol 1997, 44(5): 477.
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6. Hering, W. et al. *CNS effects of the new benzodiazepines Ro 48-6791 and Ro 48-8684 compared to midazolam in young and elderly volunteers*. Anesthesiology 1996, 85(3A): Abst A189.
7. Hering, W. et al. *Ro 48-6791, a short-acting benzodiazepine: Pharmacokinetics and pharmacodynamics in young and elderly volunteers in comparison with midazolam*. Anaesthesist 1996, 45(12): 1211.
8. Sá Rêgo, M.M. et al. *A comparison of Ro 48-6791, a novel benzodiazepine, to midazolam for sedation during ambulatory surgery under local or regional anesthesia*. Anesthesiology 1997, 87(3A, Suppl.): Abst A13.
9. Tang, J. et al. *Comparison of the recovery profiles of Ro 48-6791, a new benzodiazepine, and midazolam when used for sedation in the ambulatory setting*. Anesthesiology 1997, 87(3A, Suppl.): Abst A14.

RO-48-8684

239169

3-[5-(Dipropylaminomethyl)oxazol-2-yl]-8-fluoro-5-methyl-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one



C22-H26-F-N5-O2; Mol wt: 411.48

ACTION – Water-soluble full agonist at the benzodiazepine receptor that is being developed as a sedative/hypnotic. In double-blind phase I studies in healthy subjects, compound was shown to cause dose-dependent sedation in a manner similar to midazolam, while having a considerably shorter duration of action; similar results were observed in studies in young and elderly volunteers. Its profile offers advantages over midazolam in terms of improved control and faster recovery.

SOURCE – Roche.

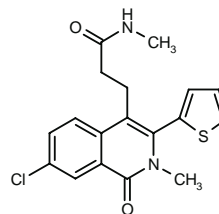
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ANXIOLYTICS

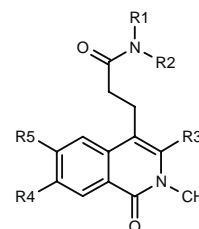
261164

3-[7-Chloro-2-methyl-1-oxo-3-(2-thienyl)-1,2-dihydro-isoquinolin-4-yl]-*N*-methylpropanamide



C18-H17-Cl-N2-O2-S; Mol wt: 360.86

ACTION – Agent with high affinity for ω (benzodiazepine) receptors associated with GABA_A receptors containing the α 3 and α 5 subunits (IC₅₀ in the range 2-20 nM), and moderate or weak affinity for ω ₁ receptors associated with GABA_A receptors containing the α 1 subunit and ω ₂ receptors associated with GABA_A receptors containing mainly α 2 and α 3 subunits. Potentially useful for disorders of GABAergic transmission such as anxiety, cognitive disorders, depression, sleep disorders, hormonal disorders related to hypothalamic dysfunction, pain and muscle spasms. Within this series of 1-oxo-1,2-dihydroisoquinoline-4-propanamide derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
261817	Me	H	3-thienyl	Cl	H	C ₁₈ H ₁₇ ClN ₂ O ₂ S
261818	Me	H	2-furyl	Cl	Me	C ₁₉ H ₁₉ ClN ₂ O ₃
261819	Me	H	2-furyl	H	Me	C ₁₉ H ₂₀ N ₂ O ₃
261820	Et	Et	2-furyl	H	Me	C ₂₂ H ₂₆ N ₂ O ₃

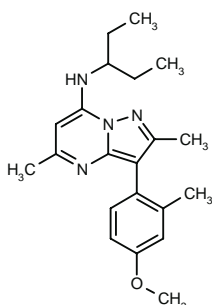
SOURCE – Synthélabo.

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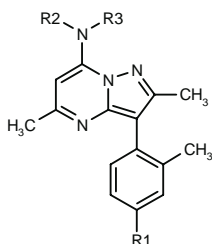
261547

7-(1-Ethylpropylamino)-3-(4-methoxy-2-methylphenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidine



C₂-H₂₈-N₄-O; Mol wt: 124.27

ACTION – Anxiolytic agent and antidepressant, a corticotropin-releasing factor (CRF) antagonist. Within this series of specifically claimed azolo triazines and pyrimidines, the following are also included:



Compound	R1	R2	R3	Formula
262371	OMe	Et	Et	C ₂₀ H ₂₆ N ₄ O
262372	Me	(CH ₂) ₃ CN	Pr	C ₂₃ H ₂₉ N ₅

SOURCE – DuPont Merck.

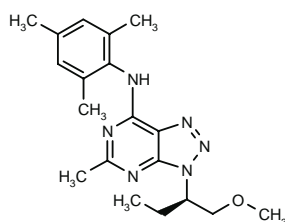
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SJ-948

262299

N-[3-[1(*R*)-(Methoxymethyl)propyl]-5-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-yl]-*N*-(2,4,6-trimethylphenyl)-amine



C₁₉-H₂₆-N₆-O; Mol wt: 354.45

ACTION – Corticotropin-releasing factor (CRF) receptor CRF₁ antagonist ($K_i = 14.2$ nM using human receptor) expected to represent an improved treatment for anxiety and/or depression. It showed an oral bioavailability of about 25% in dogs.

SOURCE – DuPont Merck.

REFERENCES

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ANTIPSYCHOTIC DRUGS

SDZ-MAR-327*

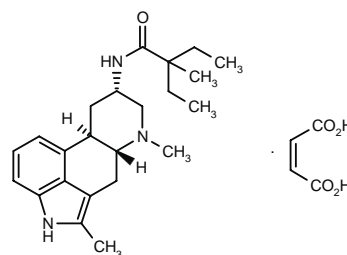
193864

147568 (as free base)

(6 α ,9 α ,10 α)-*N*-(5,7-Dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl)-2-ethyl-2-methylbutyramide monomaleate

trans-N-[(8 α)-2,6-Di-methylergolin-8-yl]-2-ethyl-2-methylbutyramide monomaleate

MAR-327



C₂₃-H₃₃-N₃-O.C₄-H₄-O₄; Mol wt: 483.61

ACTION – Atypical antipsychotic agent, a high-potency, low-efficacy partial dopamine D₂ receptor agonist shown to possess additional D₁ receptor-antagonist activity in preclinical studies. However, no significant binding to D₁ receptors was observed in healthy humans following a single oral dose of 9 mg of compound, as assessed by positron emission tomography. It is being evaluated in phase II trials as a treatment for schizophrenia.

SOURCE – Novartis.

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2. Anand, R. et al. *Determination of the maximum tolerated dose of SDZ MAR 327 in schizophrenic patients*. IBC 1st Int Symp Schizophrenia (May 8-9, Philadelphia) 1995.
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6. Fukaya, H. et al. *Effects of SDZ MAR 327 on the 5-HT receptor subtypes mediated behavioral responses in rat*. Jpn J Pharmacol 1995, 67(Suppl. 1): Abst P2-225.

7. Fukaya, K. et al. *Effect of SDZ MAR 327 on rats behavior, induced by 5-HT₂ receptor*. 24th Annu Meet Jpn Soc Neuropsychopharmacol (Oct 20-21, Okayama) 1994, Abst D-35.

8. Habucky, K. et al. *Pharmacokinetics (PK) of SDZ 3H-MAR 327 (M) following oral administration to humans*. Pharm Res 1994, 11(10, Suppl.): Abst PPDM 8267.

9. Jin, Y. et al. *Changes in EEG resonance following SDZ MAR 327 treatment*. Biol Psychiat 1995, 37(9): Abst 272.

10. Lieberman, J.A. *Atypical antipsychotic drugs as a first-line treatment of schizophrenia: A rationale and hypothesis*. J Clin Psychiatry 1996, 57(Suppl. 11): 68.

11. Markstein, R. et al. *Dopamine blockade and atypical neuroleptics*. 7th Int Catecholamine Symp (June 22-26, Amsterdam) 1992, Abst.

12. Markstein, R. et al. *SDZ MAR-327, a novel potential antipsychotic agent*. Dopamine '92 Neurobiol Neuropathol (May 16-20, S. Margherita di Pula) 1992, 125.

13. Meltzer, L. et al. *Preclinical pharmacology of dopamine partial agonists*. Eur Neuropsychopharmacol 1996, 6(Suppl. 3): Abst S-2-4.

14. Potkin, S.G. et al. *Functional neuroimaging to evaluate atypical antipsychotic compounds: an FDG PET study of SDZ MAR 327*. Eur Neuropsychopharmacol 1995, 5(3): Abst S-28-6.

15. Potkin, S. et al. *Neuroimaging to evaluate atypical antipsychotic compounds: An FDG PET study of SDZ MAR 327*. Eur Neuropsychopharmacol 1996, 6(Suppl. 3): Abst S-2-3.

16. Seno, N. et al. *Partially inhibitory effects of SDZ MAR 327 on substantia nigra dopamine neurons in rat midbrain slices*. Jpn J Pharmacol 1996, 71(Suppl. 1): Abst P-464.

17. Wang, T. and Tse, F.L.S. *Estimation of tritiated water formation following multiple oral doses of a tritium-labeled compound*. J Pharm Sci 1998, 87(1): 123.

18. *In development: New medicines for mental illnesses*. Pharmaceutical Research and Manufacturers of America 1996, April.

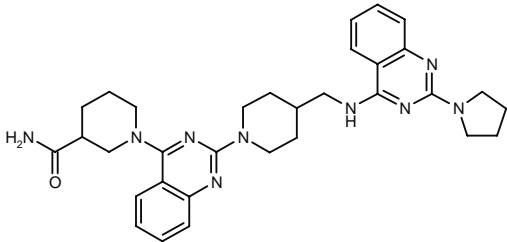
19. *Novartis' R&D pipeline*. Prous Science Daily Essentials July 14, 1997.

*Identified compound **147568** Drug Data Rep 1989, 11(4): 260.

ANTIDEPRESSANTS

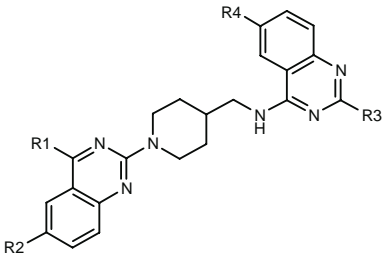
262348

1-[2-[4-[2-(1-Pyrrolidinyl)quinazolin-4-ylaminomethyl]-piperidin-1-yl]quinazolin-4-yl]piperidine-3-carboxamide

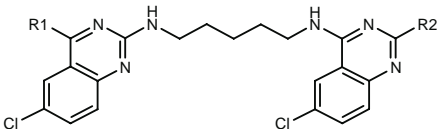


C32-H39-N9-O; Mol wt: 565.72

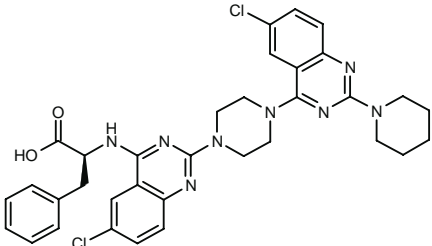
ACTION – Agent for the treatment of CNS disorders, particularly depression, that acts by blocking apamine-sensitive potassium channels, as demonstrated in binding assays ($K_i = 150$ nM against [125 I]-apamine binding in bovine cerebral membrane preparations). Within this series of 2,4'-bridged bis-2,4-diaminoquinazolines, the following are also included:



Compound	R1	R2	R3	R4	Formula
262792	4-CO2H-1-Pip	Cl	4-Me-1-Pip	Cl	C ₃₄ H ₄₀ Cl ₂ N ₈ O ₂
262793	4-(NH2CO)-1-Pip	H	4-Me-1-Pip	H	C ₃₄ H ₄₃ N ₉ O
262795	-L-Ala-NH2	Cl	1-Pip	Cl	C ₃₀ H ₃₅ Cl ₂ N ₉ O
262797	3-(NH2CO)-1-Pip	Cl	1-pyrrolidinyl	Cl	C ₃₂ H ₃₇ Cl ₂ N ₉ O



Compound	R1	R2	Formula
262794	4-(NH2CO)-1-Pip	1-pyrrolidinyl	C ₃₁ H ₃₇ Cl ₂ N ₉ O
262798	4-(NH2CO)-PhCH2NH	4-(cyclohexyl)-1-Piz	C ₃₉ H ₄₆ Cl ₂ N ₁₀ O



262791: C34-H34-Cl2-N8-O2

SOURCE – Bayer.

REFERENCES

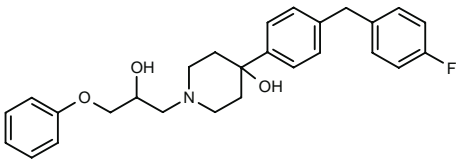
1. Schohe-Loop, R. et al. (Bayer AG) *2,4'-Bridged bis-2,4-diaminoquinazolines*. US 5739127.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

261519

1-[4-[4-(4-Fluorobenzyl)phenyl]-4-hydroxypiperidin-1-yl]-3-phenoxy-2-propanol



C27-H30-F-N-O3; Mol wt: 435.54

5. Diamond, B. et al. *SDZ MAR 327: Establishing an MTD for a putative novel antipsychotic agent*. Psychopharmacol Bull 1996, 32(3): 432.

6. Fukaya, H. et al. *Effects of SDZ MAR 327 on the 5-HT receptor subtypes mediated behavioral responses in rat*. Jpn J Pharmacol 1995, 67(Suppl. 1): Abst P2-225.

7. Fukaya, K. et al. *Effect of SDZ MAR 327 on rats behavior, induced by 5-HT₂ receptor*. 24th Annu Meet Jpn Soc Neuropsychopharmacol (Oct 20-21, Okayama) 1994, Abst D-35.

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9. Jin, Y. et al. *Changes in EEG resonance following SDZ MAR 327 treatment*. Biol Psychiat 1995, 37(9): Abst 272.

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13. Meltzer, L. et al. *Preclinical pharmacology of dopamine partial agonists*. Eur Neuropsychopharmacol 1996, 6(Suppl. 3): Abst S-2-4.

14. Potkin, S.G. et al. *Functional neuroimaging to evaluate atypical antipsychotic compounds: an FDG PET study of SDZ MAR 327*. Eur Neuropsychopharmacol 1995, 5(3): Abst S-28-6.

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17. Wang, T. and Tse, F.L.S. *Estimation of tritiated water formation following multiple oral doses of a tritium-labeled compound*. J Pharm Sci 1998, 87(1): 123.

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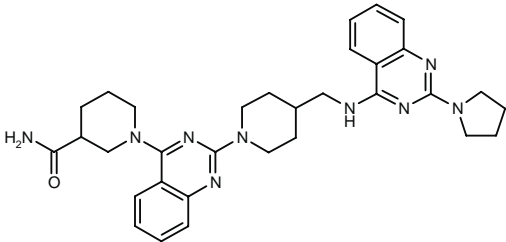
19. *Novartis' R&D pipeline*. Prous Science Daily Essentials July 14, 1997.

*Identified compound **147568** Drug Data Rep 1989, 11(4): 260.

ANTIDEPRESSANTS

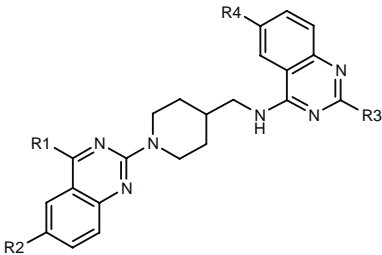
262348

1-[2-[4-[2-(1-Pyrrolidinyl)quinazolin-4-ylaminomethyl]-piperidin-1-yl]quinazolin-4-yl]piperidine-3-carboxamide

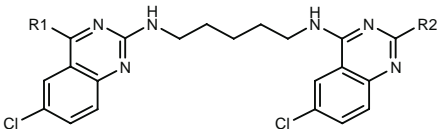


C32-H39-N9-O; Mol wt: 565.72

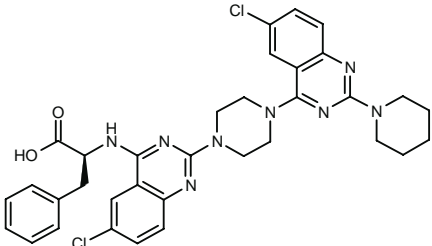
ACTION – Agent for the treatment of CNS disorders, particularly depression, that acts by blocking apamine-sensitive potassium channels, as demonstrated in binding assays (K_i = 150 nM against [¹²⁵I]-apamine binding in bovine cerebral membrane preparations). Within this series of 2,4'-bridged bis-2,4-diaminoquinazolines, the following are also included:



Compound	R1	R2	R3	R4	Formula
262792	4-CO2H-1-Pip	Cl	4-Me-1-Pip	Cl	C ₃₄ H ₄₀ Cl ₂ N ₈ O ₂
262793	4-(NH2CO)-1-Pip	H	4-Me-1-Pip	H	C ₃₄ H ₄₃ N ₉ O
262795	-L-Ala-NH2	Cl	1-Pip	Cl	C ₃₀ H ₃₅ Cl ₂ N ₉ O
262797	3-(NH2CO)-1-Pip	Cl	1-pyrrolidinyl	Cl	C ₃₂ H ₃₇ Cl ₂ N ₉ O



Compound	R1	R2	Formula
262794	4-(NH2CO)-1-Pip	1-pyrrolidinyl	C ₃₁ H ₃₇ Cl ₂ N ₉ O
262798	4-(NH2CO)-PhCH2NH	4-(cyclohexyl)-1-Piz	C ₃₉ H ₄₆ Cl ₂ N ₁₀ O



262791: C34-H34-Cl2-N8-O2

SOURCE – Bayer.

REFERENCES

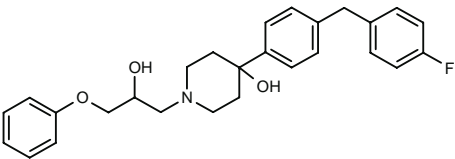
1. Schohe-Loop, R. et al. (Bayer AG) *2,4'-Bridged bis-2,4-diaminoquinazolines*. US 5739127.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

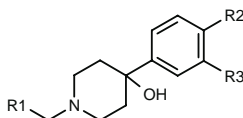
261519

1-[4-[4-(4-Fluorobenzyl)phenyl]-4-hydroxypiperidin-1-yl]-3-phenoxy-2-propanol



C27-H30-F-N-O3; Mol wt: 435.54

ACTION – Agent for the treatment of ischemic disorders and epilepsy that blocks T-type calcium and sodium channels. Compound produced 18.7% inhibition of veratridine-induced activation of sodium channels in rat cerebral cortex at 0.1 μ M, and it inhibited T-type Ca^{2+} channels in rat hippocampal CA1 cells with an IC_{50} value of 1.3 μ M. *In vivo*, it produced 90% inhibition of audiogenic seizures in mice at 10 mg/kg i.p. Within this series of arylpiperidinol and arylpiperidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
262688	CH=CHPh	Ph	F	$\text{C}_{26}\text{H}_{26}\text{FNO}$
262689	COPh	Ph	F	$\text{C}_{25}\text{H}_{24}\text{FNO}_2$
262690	CH=CHPh	OPh	H	$\text{C}_{26}\text{H}_{27}\text{NO}_2$
262691	(S)-CH(OH)CH ₂ OPh	Ph	F	$\text{C}_{26}\text{H}_{26}\text{FNO}_3$
262692	(R)-CH(OH)CH ₂ OPh	Ph	F	$\text{C}_{26}\text{H}_{26}\text{FNO}_3$

SOURCE – Suntory.

REFERENCES

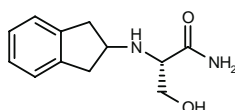
1. Annoura, H. et al. (Suntory, Ltd.) *Arylpiperidinol and arylpiperidine derivs. and drugs containing the same*. WO 9803172.

CHF-2993

261531

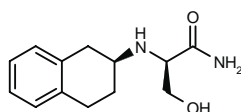
3-Hydroxy-2-(S)-(indan-2-ylamino)propionamide

N-(2-Indanyl)-L-serinamide

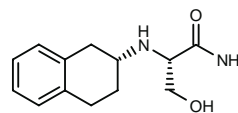


C₁₂-H₁₆-N₂-O₂; Mol wt: 220.27

ACTION – Anticonvulsant whose activity was assessed in the maximal electroshock (MES) test in mice (ED_{50} = 44 mg/kg p.o.), with greater potency and a longer duration of action than milacemide. It showed low neurotoxic potential, as evaluated in the horizontal screen test in mice (TD_{50} = 1172 mg/kg p.o.). Compound was also active in the MES test in rats (ED_{50} = 31 mg/kg p.o.), with a duration of action of 6 h, and protected against bicuculline-induced convulsions in mice (ED_{50} = 65 mg/kg p.o.). It exhibited activity comparable to that of standard antiepileptic drugs including phenytoin, carbamazepine and sodium valproate, but a higher therapeutic index. It is also potentially useful for the treatment of Alzheimer's disease, dementia, Parkinson's disease, Huntington's disease, stroke, head injury and depression. Other representative compounds within this series of α -amino acid amides include the following:



CHF-2983 [262507]: C₁₃-H₁₈-N₂-O₂



CHF-2991 [262508]: C₁₃-H₁₈-N₂-O₂

SOURCE – Chiesi.

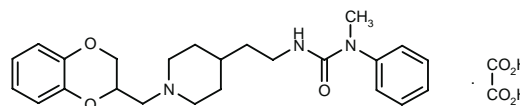
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

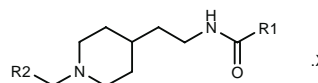
261222

N-[2-[1-(1,4-Benzodioxan-2-ylmethyl)piperidin-4-yl]ethyl]-N'-methyl-N'-phenylurea oxalate



C₂₄-H₃₁-N₃-O₃.C₂-H₂-O₄; Mol wt: 499.56

ACTION – Agent for the treatment of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, as well as depression, attention deficit hyperactivity disorder, cerebral and myocardial ischemia, stroke, peripheral myopathy and male sexual dysfunction, a potent α_2 -adrenoceptor antagonist (IC_{50} = 1.1 nM). *In vivo*, it stimulated the release of norepinephrine at the central level, as demonstrated by inhibition of guanabenz-induced hypothermia in mice (ED_{50} = 0.02 mg/kg i.p., 0.09 mg/kg p.o.). Within this series of benzodioxanes and benzopyranes, the following are also included:



Compound	R1	R2	R3	Formula
261978	NHPh	1,4-benzodioxan-2-yl	fumarate	$\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3$.C ₄ H ₄ O ₄
261979	N(Me) ₂	1,4-benzodioxan-2-yl		$\text{C}_{19}\text{H}_{28}\text{N}_3\text{O}_3$
261980	2-Cl-PhNH	1,4-benzodioxan-2-yl	oxalate	$\text{C}_{23}\text{H}_{28}\text{ClN}_3\text{O}_3$.C ₂ H ₂ O ₄
261981	1-Naph-NH	1,4-benzodioxan-2-yl	oxalate	$\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_3$.C ₂ H ₂ O ₄
261982	NHCOPh	1,4-benzodioxan-2-yl	oxalate	$\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_4$.C ₂ H ₂ O ₄
261983	NHPh	2-Me-1,4-benzodioxan-2-yl	fumarate	$\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3$.C ₄ H ₄ O ₄
261984	NHPh	2-3-dihydro-2-benzofuryl	oxalate	$\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2$.C ₂ H ₂ O ₄
261985	NHPh	2H-1-benzopyran-3-yl	HCl	$\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_2$.HCl

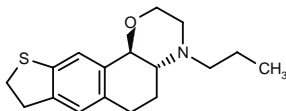
SOURCE – Pierre Fabre.

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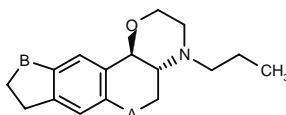
261900

trans-4-Propyl-3,4,4a,5,6,8,9,11b-octahydro-2*H*-thieno-[3',2':6,7]naphtho[1,2-*b*][1,4]oxazine



C17-H23-N-O-S; Mol wt: 289.43

ACTION – Agent for the treatment of Parkinson's disease, memory disorders, drug abuse, depression and psychoses that exhibits high affinity and selectivity for dopamine D₃ receptors relative to D₂ receptors. Other related compounds include the following:



Compound	A	B	Formula
262003	O	CO	C ₁₇ H ₂₁ NO ₃
262004	CH ₂	SO	C ₁₇ H ₂₃ NO ₂ S

SOURCE – ADIR.

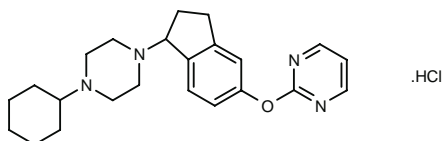
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COGNITION-ENHANCING DRUGS

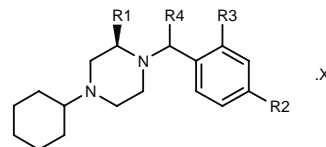
261160

1-Cyclohexyl-4-[5-(2-pyrimidinylloxy)indan-1-yl]piperazine hydrochloride



C23-H30-N4-O.HCl; Mol wt: 414.98

ACTION – Agent for the treatment of cognitive and neurodegenerative disorders such as Alzheimer's disease, a muscarinic receptor antagonist with selectivity for M₂ (K_i = 11.5 nM) and M₄ (K_i = 17 nM) receptors over M₁ receptors (K_i = 151 nM; M₁/M₂ ratio = 13.2). Also claimed are synergistic combinations with acetylcholinesterase inhibitors. Other specifically claimed compounds from this series of di-*N*-substituted piperazines and 1,4-disubstituted piperidines include the following:



Compound	R1	R2	R3	R4	X	Isomer	Formula
261813	H	2-pyrimidinyl-O	-(CH ₂) ₃ -		dimaleate		C ₂₄ H ₃₂ N ₄ O .2C ₄ H ₄ O ₄
261814	H	2-pyrimidinyl-O	-(CH ₂) ₂ -		dimaleate		C ₂₃ H ₃₀ N ₄ O .2C ₄ H ₄ O ₄
261815	Me	4-MeO- -PhSO ₂	-(CH ₂) ₂ -		HCl	A	C ₂₇ H ₃₆ N ₂ O ₃ S .HCl
261816	Me	4-MeO- -PhSO ₂	-(CH ₂) ₂ -		HCl	B	C ₂₇ H ₃₆ N ₂ O ₃ S .HCl

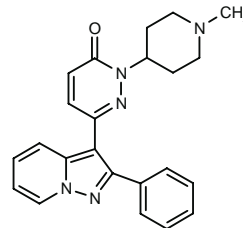
SOURCE – Schering Corp.

REFERENCES

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261545

2-(1-Methylpiperidin-4-yl)-6-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3(2*H*)-one



C23-H23-N5-O; Mol wt: 385.47

ACTION – Adenosine A₁ receptor antagonist, as demonstrated in a binding assay by > 90% inhibition of [³H]-DPCPX binding to human A₁ receptors at 0.1 μM. Potentially useful for the treatment or prevention of dementia, depression, anxiety, pain, stroke and heart failure.

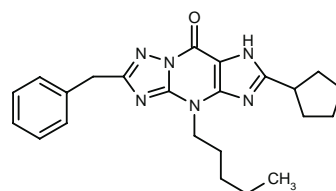
SOURCE – Fujisawa.

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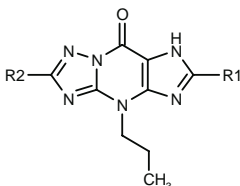
261548

6-Benzyl-2-cyclopentyl-4-pentyl-4,9-dihydro-1*H*-[1,2,4]-triazolo[1,5-*a*]purin-9-one



C23-H28-N6-O; Mol wt: 404.51

ACTION – Adenosine receptor antagonist with selective affinity for human A₁ (K_i = 10.3 nM) and A₃ (K_i = 26 nM) adenosine receptors as compared to rat A₂ receptors (K_i = 1231 nM). Potentially useful for the treatment of neurodegenerative disorders such as Alzheimer's disease, depression, asthma, allergic rhinitis, urticaria, arthritis, cardiovascular disorders and as a diuretic. Within this series of triazolopurines, the following are also included:



Compound	R1	R2	Formula
262273	Et	CH2Ph	C ₁₈ H ₂₀ N ₆ O
262274	cyclopentyl	CH2Ph	C ₂₁ H ₂₄ N ₆ O
262275	cyclopentyl	Pr	C ₁₇ H ₂₄ N ₆ O
262276	cyclopentyl	2-furyl	C ₁₈ H ₂₀ N ₆ O ₂
262277	N(Me)2	CH2Ph	C ₁₈ H ₂₁ N ₇ O

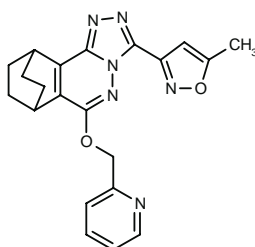
SOURCE – Boehringer Ingelheim.

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1. Küfner-Mühl, U. et al. (Boehringer Ingelheim KG) *New triazolopurines, method of preparing them and their use as drugs*. WO 9803511.

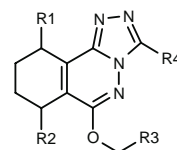
261587

3-(5-Methylisoxazol-3-yl)-6-(2-pyridylmethoxy)-7,10-ethano-7,8,9,10-tetrahydro-1,2,4-triazolo[3,4-a]-phthalazine



C₂₁H₂₀N₆O₂; Mol wt: 388.43

ACTION – Agent for the treatment of cognition disorders, a potent inverse agonist of the GABA_A α5 receptor subtype (K_i = 25 nM or less against [³H]-flumazenil binding to the α5 subunit of the human GABA_A receptor stably expressed in Ltk cells), relatively free of activity at α1, α2 and/or α3 subtypes and thus expected to be devoid of the proconvulsant effects of benzodiazepine receptor partial or full inverse agonists. Other specifically claimed compounds from this series of triazolopyridazine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
262580	-(CH2)2-		2-CN-Ph	5-Me-3-isoxazolyl	C ₂₃ H ₂₀ N ₆ O ₂
262581	-(CH2)2-		3-Me-2-Pyr	2-pyrazinyl	C ₂₂ H ₂₁ N ₇ O
262582	-(CH2)2-		2-Pyr	2-pyrazinyl	C ₂₁ H ₁₉ N ₇ O
262583	-CH2-		2-Pyr	5-Me-3-isoxazolyl	C ₂₀ H ₁₈ N ₆ O ₂
262584	-CH2-		6-Me-2-Pyr	5-Me-3-isoxazolyl	C ₂₁ H ₂₀ N ₆ O ₂
262585	-CH2-		2-Pyr	3-furyl	C ₂₀ H ₁₇ N ₅ O ₂

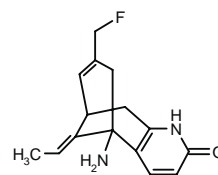
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme, Ltd.) *Subst. triazolo pyridazine derivs. as inverse agonists of the GABA_Aα5 receptor subtype*. WO 9804560.

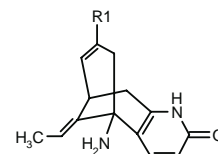
261853

5-Amino-11(*E*)-ethylidene-7-(fluoromethyl)-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]pyridine-2(1*H*)-one



C₁₅H₁₇F-N₂O; Mol wt: 260.31

ACTION – Agent for the treatment of cognition disorders such as Alzheimer's disease, an inhibitor of acetylcholinesterase (AChE; IC₅₀ = 0.2 μM in rat brain preparations). Other related compounds include the following:



Compound	R1	Formula
262746	CO ₂ Et	C ₁₇ H ₂₀ N ₂ O ₃
262747	CH ₂ OH	C ₁₅ H ₁₈ N ₂ O ₂

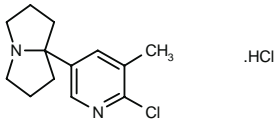
SOURCE – Sagami.

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1. Terajima, S. et al. (Sagami Chem. Res. Center) *(11E)-5-Amino-11-ethylidene-5,6,9,10-tetrahydro-5,9-methanocycloocta[b]pyridine-2(1H)-one derivs. and their intermediates*. JP 98036352.

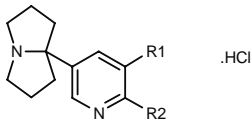
261902

7a-(6-Chloro-5-methylpyridin-3-yl)perhydropyrrolizine hydrochloride



C13-H17-Cl-N2.HCl; Mol wt: 273.20

ACTION – Potent and selective neuronal nicotinic acetylcholine receptor (nAChR) ligand giving a K_i value of 0.05 nM when tested *in vitro* for its ability to bind to nAChRs in crude synaptic membrane preparations from whole rat brain using [3 H]-cytisine as the radioligand. Its ability to interact with nAChRs was also demonstrated *in vitro* in human neuroblastoma IMR-32 cells, giving 91% activation response in the $^{86}\text{Rb}^+$ efflux assay relative to that elicited by 100 μM (*S*)-nicotine at a concentration of 1 μM . Within this series of 7a-substituted hexahydro-1*H*-pyrrolizine compounds, the following are also included:



Compound	R1	R2	Formula
261996	H	Cl	C ₁₂ H ₁₅ ClN ₂ .HCl
261997	Cl	Cl	C ₁₂ H ₁₄ Cl ₂ N ₂ .HCl
261998	H	Me	C ₁₃ H ₁₈ N ₂ .HCl

SOURCE – Abbott.

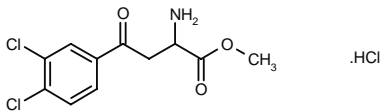
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1. Wasicak, J.T. et al. (Abbott Labs.) 7a-Heterocycle subst. hexahydro-1*H*-pyrrolizine cpds. useful in controlling chemical synaptic transmission. US 5733912.

PNU-157678

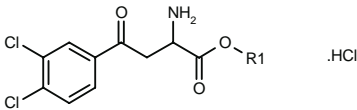
261530

2-Amino-4-(3,4-dichlorophenyl)-4-oxobutyric acid methyl ester hydrochloride



C11-H11-Cl2-N-O3.HCl; Mol wt: 312.58

ACTION – Agent for the treatment of neurodegenerative disorders including Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, epilepsy and dementia that acts as a kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) inhibitor, as demonstrated *in vitro* in rat liver mitochondrial extracts (IC_{50} = 0.51 μM). It is reported to have good aqueous solubility. Other representative compounds within this series of benzoylpropionic acid ester derivatives include the following:



Compound	R1	Isomer	Formula
PNU-161145 [262363]	Me	S	C ₁₁ H ₁₁ Cl ₂ NO ₃ .HCl
PNU-161144 [262364]	Me	R	C ₁₁ H ₁₁ Cl ₂ NO ₃ .HCl
PNU-161250 [262365]	Et		C ₁₂ H ₁₃ Cl ₂ NO ₃ .HCl
PNU-161248 [262366]	i-Pr		C ₁₃ H ₁₅ Cl ₂ NO ₃ .HCl
PNU-161252 [262367]	CH2Ph		C ₁₇ H ₁₅ Cl ₂ NO ₃ .HCl

SOURCE – Pharmacia & Upjohn.

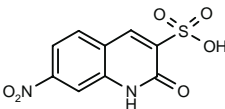
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1. Varasi, M. et al. (Pharmacia & Upjohn SpA) Benzoylpropionic acid ester derivs. WO 9803469.

TREATMENT OF Cerebrovascular diseases

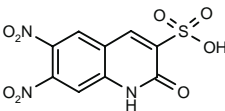
260865

7-Nitro-2-oxo-1,2-dihydroquinoline-3-sulfonic acid



C9-H6-N2-O6-S; Mol wt: 270.22

ACTION – Neuronal injury inhibitor that acts by blockade of AMPA excitatory amino acid receptors. It protected rats from glutamate-dependent audiogenic seizures (ED_{50} = 26.9 mg/kg i.p.; 80% inhibition of mortality at 50 mg/kg i.p.). At 20 mg/kg i.v., test compound reduced cortical infarct volume by 45% in rats subjected to middle cerebral artery occlusion; a decrease in final infarct volume of 44% was found when compound was given at 10 mg/kg i.p. b.i.d. for 3 days following the initial i.v. injection. Another specifically claimed 2(1*H*)-quinolinone derivative is:



261331: C9-H5-N3-O8-S

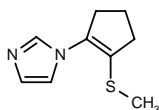
SOURCE – ADIR.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) 2-(1*H*)-Quinolone derivs. as antagonists of excitatory amino acids. EP 818449, JP 98067747.

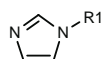
261167

1-[2-(Methylsulfanyl)-1-cyclopentenyl]imidazole



C₉-H₁₂-N₂-S; Mol wt: 180.27

ACTION – Agent for the treatment of neurodegenerative, inflammatory, autoimmune and cardiovascular disorders, an inhibitor of inducible nitric oxide synthase (iNOS). Other specifically claimed compounds from this series of imidazole derivatives include the following:



Compound	R1	Formula
261797	2-(2-thienyl)-1-cyclopentenyl	C ₁₂ H ₁₂ N ₂ S
261798	3-MeS-2-thienyl	C ₈ H ₈ N ₂ S ₂
261799	4-(2-thienyl)-2-thienyl	C ₁₁ H ₈ N ₂ S ₂

SOURCE – Schering AG.

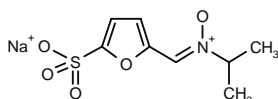
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- Hölscher, P. et al. (Schering AG) *Imidazol derivs. useful as nitrogen monoxide synthase inhibitors*. WO 9800430.

261541

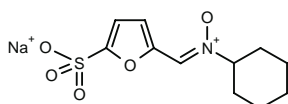
5-(N-Isopropyliminomethyl)furan-2-sulfonic acid N-oxide sodium salt

N-Isopropyl(5-sulfofuran-2-yl)nitron sodium salt



C₈-H₁₀-N-Na-O₅-S; Mol wt: 255.22

ACTION – Agent for the treatment of stroke, myocardial infarction, neurodegenerative disorders, autoimmune diseases and inflammatory disorders with free radical-scavenging activity, as demonstrated in several *in vitro* tests, and reported to possess very low toxicity. *In vivo*, it reduced mean infarct volume by 32% when administered at 10 mg/kg i.v. 3 h following permanent middle cerebral artery occlusion in rats. It was also able to inhibit various *in vitro* and *in vivo* effects of amyloid β -peptide and to reduce neuronal inflammation. Compound was also effective in a myelin basic protein (MBP)-induced experimental allergic encephalomyelitis model in rats. Another specifically claimed furan nitron compound is:



262238: C₁₁-H₁₄-N-Na-O₅-S

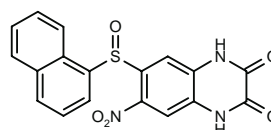
SOURCE – Centaur.

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- Kelleher, J.A. et al. (Centaur Pharm., Inc.) *Furan nitron cpds*. WO 9803496.

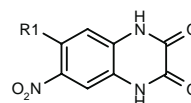
261844

6-(1-Naphthylsulfinyl)-7-nitroquinoxaline-2,3(1H,4H)-dione



C₁₈-H₁₁-N₃-O₅-S; Mol wt: 381.36

ACTION – Agent for the treatment of neurodegenerative disorders that acts by inhibiting neuronal cell death, as demonstrated in human neuroblastoma SH-SY5Y cells. Within this series of nitroquinoxalinedione derivatives, the following are also included:



Compound	R1	Formula
262727	5-isoquinolyl-SO ₂	C ₁₇ H ₁₀ N ₄ O ₆ S
262729	1-Naph-S	C ₁₈ H ₁₁ N ₃ O ₄ S

SOURCE – Snow Brand Milk Products.

REFERENCES

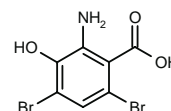
- Ishiguro, S. et al. (Snow Brand Milk Products) *Novel nitroquinoxalinedione derivs*. JP 98029985.

NCR-631*

214060

2-Amino-4,6-dibromo-3-hydroxybenzoic acid

4,6-Dibromo-3-hydroxyanthranilic acid



C₇-H₅-Br₂-N-O₃; Mol wt: 310.93

ACTION – Neuroprotective agent that acts via inhibition of 3-hydroxyanthranilate 3,4-dioxygenase (3-HAO) in the kynurenine pathway, thus inhibiting the production of the putative neurotoxin quinolinic acid. At concentrations of 10-100 μ M, it provided significant protection against anoxia-induced rat hippocampal cell loss, and at 1 μ M it counteracted the neuroinflammatory-mediated loss of hippocampal pyramidal neurons resulting from incubation with lipopolysaccharide (LPS) or IL-1 β .

SOURCES – Astra Arcus; Cornell Res. Found.; Univ. Maryland, Baltimore, MD (US).

REFERENCES

1. Björk, S.K.M. et al. (AB Astra; Univ. Maryland; Cornell Res. Found., Inc.) *New cpds.* EP 686145, JP 96509468, WO 9419316.

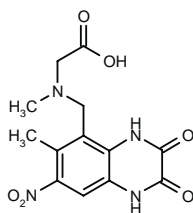
2. Luthman, J. et al. *Effects of the 3-hydroxyanthranilic acid analogue NCR-631 on anoxia, IL-1 β - and LPS-induced hippocampal pyramidal cell loss in vitro.* *Amino Acids* 1998, 14(1-3): 263.

*Identified compound **214060** Drug Data Rep 1995, 17(1): 33.

PD-159265^{2,3}

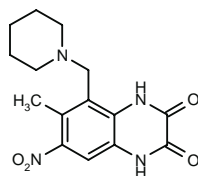
261724

N-Methyl-*N*-(6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)glycine



C13-H14-N4-O6; Mol wt: 322.28

ACTION – Neuroprotective agent, a semiconstrained analog of PNQX with improved water solubility. It acts as a glutamate receptor antagonist with affinity for AMPA receptors ($IC_{50} = 120$ nM) and lower affinity for kainate receptors ($IC_{50} = 3.48$ μ M). Another related compound is:



PD-160725¹⁻³ [261748]: C15-H18-N4-O4

SOURCE – Warner-Lambert.

REFERENCES

1. Kornberg, B.E. et al. (Warner-Lambert Co.) *Cyclic amine derivs. of substd. quinoxaline 2,3-diones as glutamate receptor antagonists.* WO 9640650.

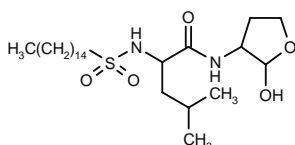
2. Kornberg, B.E. et al. *New conformationally semi-constrained AMPA receptor antagonists.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 135.

3. Nikam, S.S. et al. *Design and synthesis of new AMPA/GlyN receptor antagonists.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 014.

MISCELLANEOUS NEUROLOGIC DRUGS

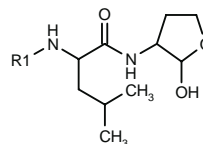
261576

N-(2-Hydroxytetrahydrofuran-3-yl)-4-methyl-2-(pentadecylsulfonamido)pentanamide



C25-H50-N2-O5-S; Mol wt: 490.74

ACTION – A potent inhibitor of cysteine proteases such as calpain ($IC_{50} = 0.09$ μ M), with potential in the treatment of muscular dystrophy, muscular atrophy, myocardial infarction, stroke, Alzheimer's disease, multiple sclerosis, cataracts, inflammation, allergy, pancreatitis, osteoporosis, hypercalcemia and cancer. Within this series of oxygen-containing heterocyclic derivatives, the following are also included:



Compound	R1	Formula
262943	COC16H33	C ₂₇ H ₅₂ N ₂ O ₄
262944	COC11H23	C ₂₂ H ₄₂ N ₂ O ₄
262945	COC14H29	C ₂₅ H ₄₈ N ₂ O ₄
262946	COC15H31	C ₂₆ H ₅₀ N ₂ O ₄
262947	COC17H35	C ₂₈ H ₅₄ N ₂ O ₄
262948	CO2C14H29	C ₂₅ H ₄₈ N ₂ O ₅
262949	SO2C16H33	C ₂₆ H ₅₂ N ₂ O ₅ S
262950	CO2C13H27	C ₂₄ H ₄₆ N ₂ O ₅
262951	SO2C14H29	C ₂₄ H ₄₈ N ₂ O ₅ S

SOURCE – Mitsubishi Chem.

REFERENCES

1. Ando, R. et al. (Mitsubishi Chem. Corp.) *Oxygenic heterocyclic derivs.* WO 9804539.

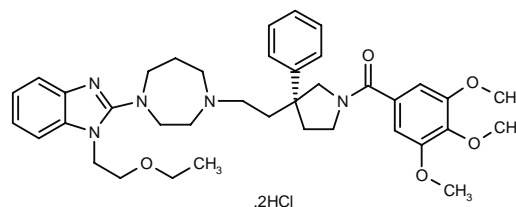
RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

MDL-108207DA

250880

(*S*)-3-[2-[4-[1-(2-Ethoxyethyl)benzimidazol-2-yl]perhydro-1,4-diazepin-1-yl]ethyl]-3-phenyl-1-(3,4,5-trimethoxybenzoyl)pyrrolidine dihydrochloride



C38-H49-N5-O5.2HCl; Mol wt: 728.76

REFERENCES

1. Björk, S.K.M. et al. (AB Astra; Univ. Maryland; Cornell Res. Found., Inc.) *New cpds.* EP 686145, JP 96509468, WO 9419316.

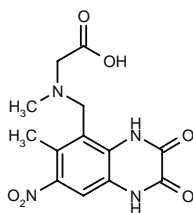
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*Identified compound **214060** Drug Data Rep 1995, 17(1): 33.

PD-159265^{2,3}

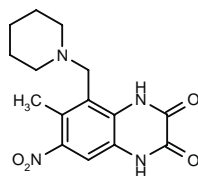
261724

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C13-H14-N4-O6; Mol wt: 322.28

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PD-160725¹⁻³ [261748]: C15-H18-N4-O4

SOURCE – Warner-Lambert.

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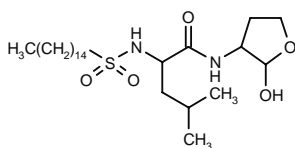
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3. Nikam, S.S. et al. *Design and synthesis of new AMPA/GlyN receptor antagonists.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 014.

MISCELLANEOUS NEUROLOGIC DRUGS

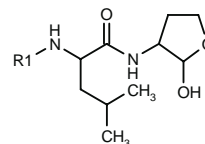
261576

N-(2-Hydroxytetrahydrofuran-3-yl)-4-methyl-2-(penta-decylsulfonamido)pentanamide



C25-H50-N2-O5-S; Mol wt: 490.74

ACTION – A potent inhibitor of cysteine proteases such as calpain ($IC_{50} = 0.09$ μ M), with potential in the treatment of muscular dystrophy, muscular atrophy, myocardial infarction, stroke, Alzheimer's disease, multiple sclerosis, cataracts, inflammation, allergy, pancreatitis, osteoporosis, hypercalcemia and cancer. Within this series of oxygen-containing heterocyclic derivatives, the following are also included:



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262945	COC14H29	C ₂₅ H ₄₈ N ₂ O ₄
262946	COC15H31	C ₂₆ H ₅₀ N ₂ O ₄
262947	COC17H35	C ₂₈ H ₅₄ N ₂ O ₄
262948	CO2C14H29	C ₂₅ H ₄₈ N ₂ O ₅
262949	SO2C16H33	C ₂₆ H ₅₂ N ₂ O ₅ S
262950	CO2C13H27	C ₂₄ H ₄₆ N ₂ O ₅
262951	SO2C14H29	C ₂₄ H ₄₈ N ₂ O ₅ S

SOURCE – Mitsubishi Chem.

REFERENCES

1. Ando, R. et al. (Mitsubishi Chem. Corp.) *Oxygenic heterocyclic derivs.* WO 9804539.

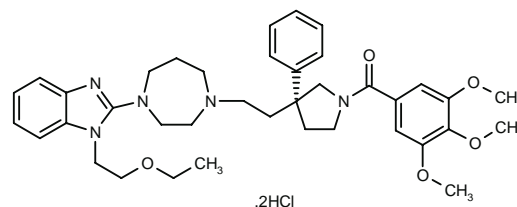
RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

MDL-108207DA

250880

(*S*)-3-[2-[4-[1-(2-Ethoxyethyl)benzimidazol-2-yl]perhydro-1,4-diazepin-1-yl]ethyl]-3-phenyl-1-(3,4,5-trimethoxybenzoyl)pyrrolidine dihydrochloride



C38-H49-N5-O5.2HCl; Mol wt: 728.76

ACTION – Agent for the treatment of allergic rhinitis, a dual histamine and substance P antagonist with good affinity for H_1 and NK_1 receptors (IC_{50} = 283 and 17 nM, respectively), and much lower affinity for NK_2 receptors (IC_{50} = 1960 nM). Compound inhibits histamine-induced contractions of isolated guinea pig ileum (pA_2 = 8) and substance P-induced inositol phosphate accumulation in cultured UC11 cells (pA_2 = 8). It also inhibits *in vivo* histamine-induced skin wheal following both i.v. and p.o. administration (ED_{50} = 0.75 and 2.0 mg/kg, respectively) and substance P-induced plasma protein extravasation in airways (ED_{50} = 0.33 and 1.9 mg/kg, respectively) in guinea pigs. It lacks significant CNS penetration, as demonstrated by its inability to modify hind limb foot tapping produced in gerbils in response to the NK_1 receptor-selective agonist GR-73632.

SOURCE – Hoechst Marion Roussel.

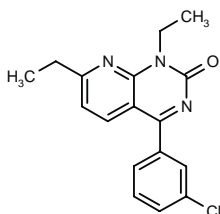
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ASTHMA THERAPY

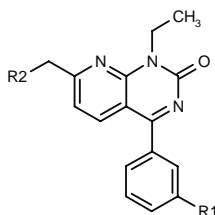
252426

4-(3-Chlorophenyl)-1,7-diethylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one



C17-H16-Cl-N3-O; Mol wt: 313.79

ACTION – Potential antiasthmatic agent, a selective inhibitor of phosphodiesterase type IV (PDE IV; IC_{50} = 0.81 nM) and the production of tumor necrosis factor (TNF- α ; IC_{50} = 6.9 nM). Compound was orally active in the carrageenan-induced pleurisy model in rats and did not cause emesis at 100 mg/kg p.o. in ferrets. Other pyridopyrimidines include the following:



Compound	R1	R2	Formula
257365	Br	Me	C ₁₇ H ₁₆ BrN ₃ O
257366	Cl	H	C ₁₆ H ₁₄ ClN ₃ O
257367	Br	H	C ₁₆ H ₁₄ BrN ₃ O

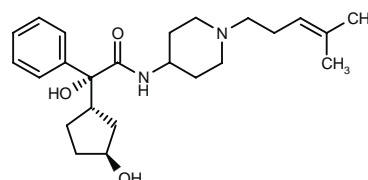
SOURCE – Yamanouchi.

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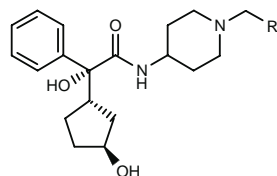
259901

2(*R*)-Hydroxy-2-[3(*S*)-hydroxy-1(*S*)-cyclopentyl]-*N*-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-phenylacetamide



C24-H36-N2-O3; Mol wt: 400.56

ACTION – Agent for the treatment of respiratory disorders such as asthma, urological disorders such as urinary incontinence and digestive disorders such as irritable bowel syndrome, a potent and selective muscarinic M_3 receptor antagonist, as demonstrated in binding studies (K_i = 18 nM vs. 90 and 2300 nM for M_1 and M_2 receptors, respectively) and in functional assays by inhibition of carbachol-induced contractions of isolated rat trachea and bladder (M_3 receptors; K_B = 10 and 19 nM, respectively) and a much weaker effect in rat right atrium (M_2 receptors; K_B = 1200 nM). *In vivo*, it inhibited acetylcholine-induced bronchoconstriction in rats upon i.v. (ID_{50} = 0.080 mg/kg) and p.o. administration (ID_{50} = 0.3 mg/kg). Within this series of 1,4-disubstituted piperidines, the following are also included:



Compound	R1	Formula
262239	cycloheptyl	C ₂₆ H ₄₀ N ₂ O ₃
262240	6-Me-2-Pyr	C ₂₅ H ₃₃ N ₃ O ₃

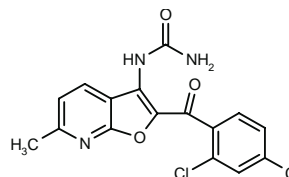
SOURCE – Banyu.

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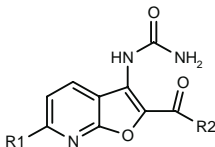
261226

N-[2-(2,4-Dichlorobenzoyl)-6-methylfuro[2,3-*b*]pyridin-3-yl]urea

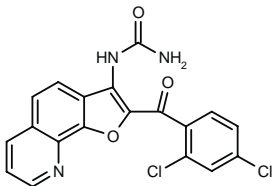


C16-H11-Cl2-N3-O3; Mol wt: 364.19

ACTION – Antiinflammatory agent that acts by inhibiting oxygen radical formation and tumor necrosis factor (TNF- α) production. Compound was found to inhibit the fMLP-stimulated production of superoxide by human polymorphonuclear leukocytes (PMN) and to inhibit TNF- α release in human monocytes stimulated with bacterial lipopolysaccharide (LPS), complement-opsonized zymosan and IL-1 β . These effects appear to be mediated by elevated cellular cAMP levels, probably due to inhibition of type IV phosphodiesterase (PDE IV). When tested *in vivo*, it reduced LPS-induced mortality in galactosamine-sensitized mice by 70-100% at doses of 3-30 mg/kg i.v. Other compounds from this series of 3-ureido-pyridofurans and -pyridothiophenes include the following:



Compound	R1	R2	Formula
261974	OH	2,4-(Cl)2-Ph	C ₁₈ H ₉ Cl ₂ N ₃ O ₄
261975	Me	2,6-(Me)2-3-Pyr	C ₁₇ H ₁₆ N ₄ O ₃
261976	Me	2,5-(Cl)2-3-thienyl	C ₁₄ H ₉ Cl ₂ N ₃ O ₃ S



261977: C₁₉-H₁₁-Cl₂-N₃-O₃

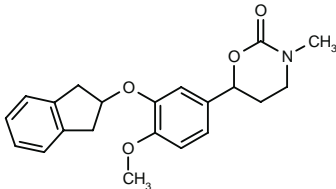
SOURCE – Bayer.

REFERENCES

1. Brunlich, G. et al. (Bayer AG) 3-Ureido-pyridofurans and -pyridothiophenes for the treatment of inflammatory processes. WO 9802440.

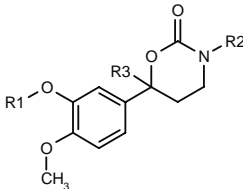
261573

6-[3-(Indan-2-yloxy)-4-methoxyphenyl]-3-methylperhydro-1,3-oxazin-2-one



C₂₁-H₂₃-N-O₄; Mol wt: 353.42

ACTION – Antiasthmatic and antiinflammatory agent, a potent inhibitor of phosphodiesterase type IV (PDE IV; IC₅₀ = 0.19 μ M against enzyme from rat neutrophils). *In vivo*, compound inhibited antigen-induced bronchoconstriction in sensitized guinea pigs with an ED₅₀ value of 0.061 mg/kg i.v. Within this series of 6-phenyltetrahydro-1,3-oxazin-2-one derivatives, the following are also included:



Compound	R1	R2	R3	Formula
262735	cyclopentyl	H	H	C ₁₆ H ₂₁ NO ₄
262736	Bu	H	H	C ₁₅ H ₂₁ NO ₄
262737	cyclopentyl	Me	Me	C ₁₈ H ₂₅ NO ₄
262738	2-indanyl	H	Me	C ₂₁ H ₂₃ NO ₄
262739	2-indanyl	Me	Me	C ₂₂ H ₂₅ NO ₄
262740	cyclopropyl-CH ₂	H	Me	C ₁₆ H ₂₁ NO ₄
262741	i-Bu	H	H	C ₁₅ H ₂₁ NO ₄
262742	i-Bu	Me	H	C ₁₆ H ₂₃ NO ₄
262743	cyclopentyl-CH ₂	H	H	C ₁₇ H ₂₃ NO ₄
262744	i-Bu	H	Me	C ₁₆ H ₂₃ NO ₄
262745	i-Bu	Me	Me	C ₁₇ H ₂₅ NO ₄

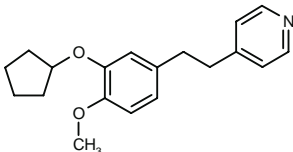
SOURCE – Nikken Chem.

REFERENCES

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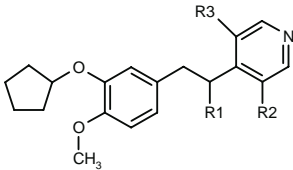
262349

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethyl]pyridine



C₁₉-H₂₃-N-O₂; Mol wt: 297.40

ACTION – Antiasthmatic, antiallergic and antiinflam-matory agent, a potent and selective inhibitor of phosphodiesterase type IV (PDE IV) with little or no activity against other PDE isozymes. Compound is reported to be orally active and to be devoid of the side effects associated with known PDE inhibitors such as rolipram. Other specifically claimed compounds within this series of trisubstituted phenyl derivatives include the following:



Compound	R1	R2	R3	Formula
262784	CN	H	H	C ₂₀ H ₂₂ N ₂ O ₂
262785	H	NHCOPh	H	C ₂₆ H ₂₈ N ₂ O ₃
262786	H	NHSO ₂ Ph	H	C ₂₅ H ₂₈ N ₂ O ₄ S
262787	H	Cl	Cl	C ₁₉ H ₂₁ Cl ₂ NO ₂
262788	H	NH ₂	H	C ₁₉ H ₂₄ N ₂ O ₂
262789	H	i-PrCONH	H	C ₂₃ H ₃₀ N ₂ O ₃
262790	H	NHCONHCH ₂ Ph	H	C ₂₇ H ₃₁ N ₃ O ₃

SOURCE – Celltech.

REFERENCES

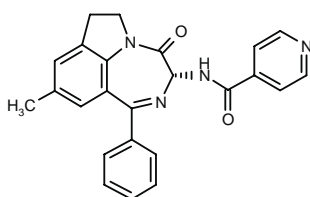
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CI-1018

261826

N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo-[3,2,1-*jk*][1,4]benzodiazepin-3(*R*)-yl]pyridine-4-carboxamide

PD-168787



C24-H20-N4-O2; Mol wt: 396.45

ACTION – Antiasthmatic agent, a phosphodiesterase type IV (PDE IV) inhibitor ($IC_{50} = 1.14 \mu M$) with high selectivity relative to PDE III ($IC_{50} > 100 \mu M$) and PDE I/V. The compound inhibited tumor necrosis factor- α (TNF- α) production from lipopolysaccharide (LPS)-stimulated human peripheral blood monocytes ($IC_{50} = 0.7 \mu M$). It was orally active against antigen-induced pulmonary eosinophilia in ovalbumin-sensitized rats ($ED_{50} = 5.1 \text{ mg/kg p.o.}$), with a duration of action of over 24 h; it was not emetic at therapeutic doses in several species.

SOURCES – Jouveinal; Warner-Lambert.

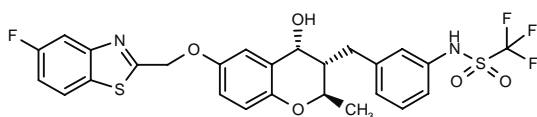
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2. Burnouf, C. et al. *Pharmacology of the novel phosphodiesterase type 4 inhibitor, CI-1018.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 008.
3. Pascal, Y. et al. *Synthesis and structure-activity relationships of 4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-hi]indolines: Novel PDE4 inhibitors.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 050.
3. Warner-Lambert Co. Annual Report 1996.

CP-195494

261777

(2*R*,3*S*,4*R*)-*N*-[3-[6-(5-Fluorobenzothiazol-2-ylmethoxy)-4-hydroxy-2-methyl-3,4-dihydro-2*H*-1-benzopyran-3-ylmethyl]phenyl]trifluoromethanesulfonamide



C26-H22-F4-N2-O5-S2; Mol wt: 582.58

ACTION – Antiasthmatic agent, a potent CysLT₁ (LTD₄) receptor antagonist with a K_i of 0.7 nM using receptors isolated from guinea pig lung membranes; the compound

blocked Ca²⁺ mobilization in human U937 cells ($IC_{50} = 8 \text{ nM}$) and antigen-induced airways obstruction in guinea pigs ($ED_{50} = 0.5 \text{ mg/kg p.o.}$), with a potency equivalent to that of zafirlukast and pranlukast.

SOURCE – Pfizer.

REFERENCES

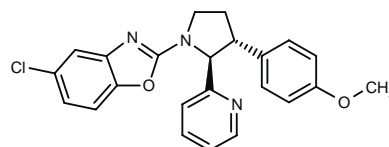
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2. Chambers, R.J. et al. *Development of new chromanol antagonists of leukotriene D₄.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 053.

BIRZ-227

262244

(2*S*,3*R*)-5-Chloro-2-[3-(4-methoxyphenyl)-2-(2-pyridyl)pyrrolidin-1-yl]benzoxazole

BIRZ-227-BS



C23-H20-Cl-N3-O2; Mol wt: 405.88

ACTION – Agent for the treatment of inflammatory disorders such as asthma, arthritis, inflammatory bowel disease and psoriasis with LTB₄-inhibitory activity. It demonstrated excellent oral bioavailability in chimpanzees (81.7% after a dose of 5.0 mg/kg by gavage), as well as a long terminal elimination half-life (20.0 h after 0.5 mg/kg by i.v. infusion).

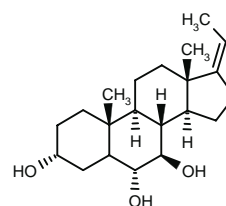
SOURCE – Boehringer Ingelheim.

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2. Alexander, J. et al. *Quantification of nanogram levels of BIRZ 227 BS: A potent LTB₄ inhibitor, by high performance liquid chromatography electrospray ionization tandem mass spectrometry in biological fluids and application for pharmacokinetic assessment in chimpanzees after i.v. and oral administration of BIRZ 227 BS.* Pharm Res 1997, 14(11, Suppl.): Abst 4217.
3. Yee, N.K. et al. *Practical synthesis of an enantiomerically pure trans-4,5-disubstituted 2-pyrrolidinone via enzymatic resolution. Preparation of the LTB₄ inhibitor BIRZ-227.* J Org Chem 1998, 63(2): 326.

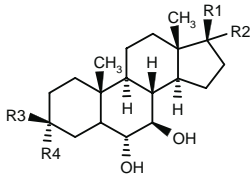
261230

(*Z*)-17,20-Didehydropregnane-3 α ,6 α ,7 β -triol



C21-H34-O3; Mol wt: 334.50

ACTION – 6,7-Oxygenated steroid with potential in the treatment or prevention of asthma, allergy, arthritis and thrombosis. Compound was found to inhibit PAF-induced rabbit platelet aggregation (20.9% inhibition at 80 μM), allergen-induced release of hexosaminidase from passively sensitized rat mast cells and murine mast cells (59 and 49% inhibition, respectively, at 25 μM), antigen-induced contractions of ileum from sensitized guinea pigs (70.0% inhibition at 30 μM) and allergen-induced contractions of trachea from sensitized guinea pigs. *In vivo*, it inhibited the allergen-induced increase in lung resistance and decrease in lung compliance in sensitized guinea pigs when administered orally at 5 mg/kg/day x 4 days or by inhalation at 50 μg/kg. In addition, it inhibited ovalbumin-induced eosinophil infiltration into broncho-alveolar lavage fluid (BALF) in rats at 5 mg/kg/day p.o. x 4 days and was effective in an allergic sheep model of asthma. Compound has also been found to inhibit NF-κB binding in rat mast cells stimulated with TPA (66% inhibition at 1 μM). Other compounds from this series of 6,7-oxygenated steroids are:



Compound	R1	R2	R3	R4	Formula
262023	Et	H	H	OH	C ₂₁ H ₃₆ O ₃
262024	-CH ₂ -		OH	H	C ₂₀ H ₃₂ O ₃

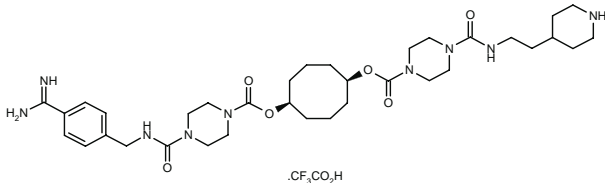
SOURCE – Inflazyme.

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1. Burgoyne, D.L. et al. (Inflazyme Pharm., Ltd.) *6,7-Oxygenated steroids and uses related thereto*. WO 9802450.

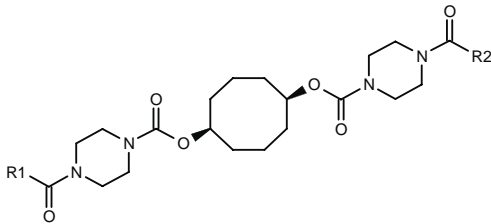
261575

4-[*N*-(4-Amidinobenzyl)carbamoyl]piperazine-1-carboxylic acid and 4-[*N*-[2-(4-piperidyl)ethyl]carbamoyl]piperazine-1-carboxylic acid mixed ester with *cis*-cyclooctane-1,5-diol trifluoroacetate



C35-H55-N9-O6.C2-H-F3-O2; Mol wt: 811.90

ACTION – Agent for the treatment of asthma and other disorders associated with inflammation of the respiratory tract that acts by virtue of its tryptase-inhibitory activity, as demonstrated in *in vitro* assays using human tryptase (K_i 0.0009 μM). *In vivo* activity was evaluated in allergic sheep, which did not exhibit late-phase bronchoconstriction or hyperresponsiveness to carbachol when treated with test compound. Other related compounds include the following:



Compound	R1	R2	Formula
262616	4-[NH ₂ C(=NH)NH]-PhCH ₂ NH	(trans)-4-NH ₂ -cyclohexyl-CH ₂ NH	C ₃₅ H ₅₆ N ₁₀ O ₆
262617	4-[NH ₂ C(=NH)NH]-PhCH ₂	4-Pip-CH ₂ CH ₂ NH	C ₃₅ H ₅₅ N ₉ O ₆
262618	4-[NH ₂ C(=NH)]-PhCH ₂	4-Pip-CH ₂ CH ₂ NH	C ₃₅ H ₅₄ N ₈ O ₆
262619	4-[NH ₂ C(=NH)]-PhCH ₂ NH	4-Pip-(CH ₂) ₃	C ₃₆ H ₅₆ N ₈ O ₆
262620	4-[NH ₂ C(=NH)]-PhCH ₂	4-Pip-(CH ₂) ₃	C ₃₆ H ₅₅ N ₇ O ₆
262621	4-[NH ₂ C(=NH)NH]-PhCH ₂ NH	4-Pip-(CH ₂) ₃	C ₃₆ H ₅₇ N ₉ O ₆
262622	4-[NH ₂ C(=NH)NH]-PhCH ₂	4-Pip-(CH ₂) ₃	C ₃₆ H ₅₆ N ₈ O ₆
262623	4-[NH ₂ C(=NH)NH]-PhCH ₂ NH	4-Pip-CH ₂ CH ₂ NH	C ₃₅ H ₅₆ N ₁₀ O ₆

SOURCE – Arris.

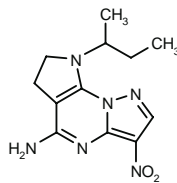
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PR-001337

262489

8-(1-Methylpropyl)-3-nitro-7,8-dihydro-6*H*-pyrazolo-[1,5-*a*]pyrrolo[3,2-*e*]pyrimidin-5-amine



C12-H16-N6-O2; Mol wt: 276.30

ACTION – Orally active antiasthmatic agent that appears to potently inhibit the immediate asthmatic reaction as compared to theophylline and cromakalin.

SOURCE – Pola.

REFERENCES

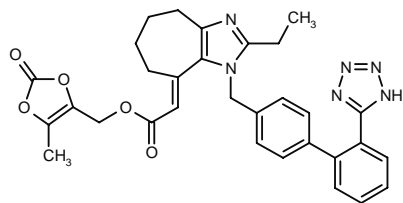
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

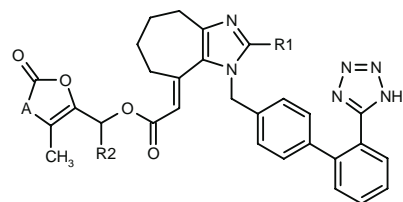
259205

2-[2-Ethyl-1-[2'-(1*H*-5-tetrazolyl)biphenyl-4-ylmethyl]-1,4,5,6,7,8-hexahydrocycloheptimidazol-8-ylidene]acetic acid 2-oxo-5-methyl-1,3-dioxol-4-ylmethyl ester



C31-H30-N6-O5; Mol wt: 566.62

ACTION – Antihypertensive agent, a potent, orally active angiotensin II (All) antagonist, as demonstrated by 70-100% inhibition of the All-induced pressor response in rats at 0.1 mg/kg p.o. Other compounds from this series of cycloheptaimidazole derivatives include the following:



Compound	R1	R2	A	Formula
261884	Me	H	O	C ₃₀ H ₂₈ N ₆ O ₅
261885	Pr	H	O	C ₃₂ H ₃₂ N ₆ O ₅
261886	Bu	H	O	C ₃₃ H ₃₄ N ₆ O ₅
261887	C5H11	H	O	C ₃₄ H ₃₆ N ₆ O ₅
261888	Et	Me	S	C ₃₂ H ₃₂ N ₆ O ₄ S
261889	Pr	Me	S	C ₃₃ H ₃₄ N ₆ O ₄ S

SOURCE – Kotobuki.

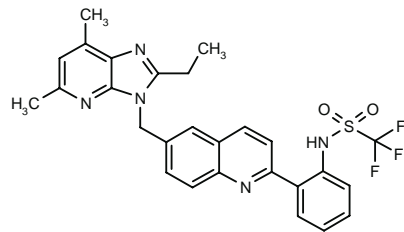
REFERENCES

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GA-0113

261726

N-[2-[6-(2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-ylmethyl)quinolin-2-yl]phenyl]trifluoromethanesulfonamide



C27-H24-F3-N5-O2-S; Mol wt: 539.57

ACTION – Antihypertensive agent, a potent, selective and competitive angiotensin II (All) AT₁ receptor antagonist (IC₅₀ = 11 nM for displacement of [¹²⁵I]-Sar¹,Ile⁸-All binding in Sf9 cells expressing human receptors) with no effect on AT₂ receptors at up to 10 μM. In isolated rabbit aortic strips, it inhibited contractions induced by All with a pD'₂ of 8.82. In conscious normotensive rats, at 0.01-1 mg/kg i.v. it inhibited the pressor response to All, whereas it had no effect on the response to norepinephrine or vasopressin. In conscious normotensive dogs, at 0.01-0.1 mg/kg p.o. it also inhibited the All-induced pressor response, with an ID₅₀ of 0.032 mg/kg. In renal hypertensive and spontaneously hypertensive rats, it decreased blood pressure after a single oral dose, with ED₂₅ values of 0.02 and 0.17 mg/kg, respectively, the effect lasting for at least 24 h after a dose of 0.1 mg/kg. Following repeated administration to spontaneously hypertensive rats (0.03-0.1 mg/kg) and renal hypertensive dogs (0.01-0.03 mg/kg), it gradually reduced blood pressure, reaching a plateau after 4 days, and its effect gradually disappeared after cessation of treatment, with no rebound phenomenon. Compound has high oral bioavailability (> 90%) and a long terminal half-life (12-25 h) in rats and dogs.

SOURCES – Asahi Glass; Green Cross (now Yoshitomi).

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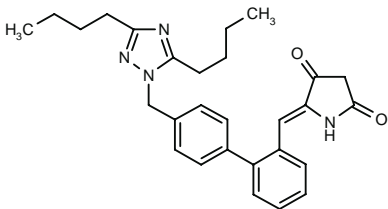
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LCY-018

261728

5(Z)-[4'-(3,5-Dibutyl-1,2,4-triazol-1-ylmethyl)biphenyl-2-ylmethylene]pyrrolidine-2,4-dione



C28-H32-N4-O2; Mol wt: 456.59

ACTION – Antihypertensive agent, an angiotensin II (All) antagonist selective for AT₁ receptors. It inhibited the angiotensin II-induced pressor response in conscious normotensive rats at i.v. doses of 0.3-10 mg/kg and reduced blood pressure in spontaneously hypertensive rats after oral administration at doses of 1-30 mg/kg.

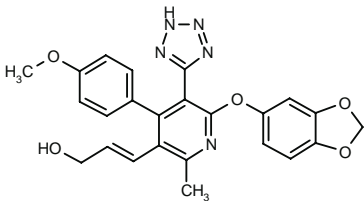
SOURCES – Lead Chem.; Toyama Med. Pharm. Univ., Toyama (JP).

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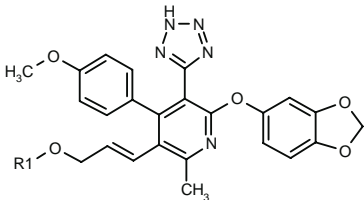
261842

2-(1,3-Benzodioxol-5-yloxy)-5-[3-hydroxy-1(E)-propenyl]-4-(4-methoxyphenyl)-6-methyl-3-(2H-5-tetrazolyl)pyridine



C24-H21-N5-O5; Mol wt: 459.46

ACTION – Endothelin (ET) receptor antagonist, as demonstrated in a binding assay using membrane fractions from pig ventricular muscle and [¹²⁵I]-ET-1 as the ligand (pIC₅₀ = 8.1). A representative compound from a series of pyridine derivatives, wherein the following are also included:



Compound	R1	Formula
262593	2-Pyr	C ₂₉ H ₂₄ N ₆ O ₅
262594	2-Pyr-NHCO	C ₃₀ H ₂₅ N ₇ O ₆
262595	2-furyl-NHCO	C ₂₉ H ₂₄ N ₆ O ₇
262596	2-Pyr-CO	C ₃₀ H ₂₄ N ₆ O ₆
262597	5-Br-2-Pyr	C ₂₉ H ₂₃ BrN ₆ O ₅

SOURCE – Ajinomoto.

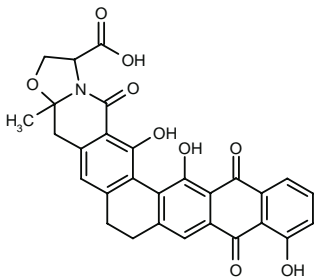
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TMC-66

262129

10,15,16-Trihydroxy-3a-methyl-9,14,17-trioxo-2,3a,4,6,7,9,14,17-octahydro-1H-naphthaceno[2,1-g]oxazolo-[3,2-b]isoquinoline-1-carboxylic acid



C29-H21-N-O9; Mol wt: 527.49

ACTION – Endothelin-converting enzyme (ECE) inhibitor obtained from a culture of *Streptomyces* sp. A-5008, with an IC₅₀ of 2.8 μM for rat pulmonary ECE.

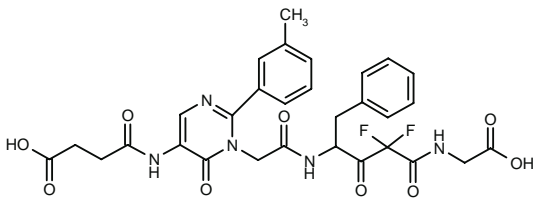
SOURCE – Tanabe Seiyaku.

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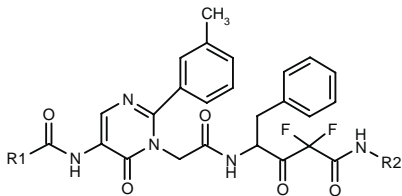
260522

N-[2,2-Difluoro-4-[2-[5-(4-hydroxysuccinylamino)-2-(3-methylphenyl)-6-oxo-1,6-dihydropyrimidin-1-yl]-acetamido]-3-oxo-5-phenylpentanoyl]glycine



C30-H29-F2-N5-O9; Mol wt: 641.58

ACTION – Agent for the treatment of angiotensin II-mediated disorders, a potent and selective inhibitor of human cardiac chymase (K_i = 0.049 μM) with no activity on human leukocyte elastase. Other compounds from this series of heterocyclic amide derivatives include the following:



Compound	R1	R2	Formula
261912	CH ₂ CH ₂ CO ₂ H	3-CO ₂ H-Ph	C ₃₅ H ₃₁ F ₂ N ₅ O ₉
261913	CH ₂ CH ₂ CO ₂ Me	CH ₂ CO ₂ H	C ₃₁ H ₃₁ F ₂ N ₅ O ₉
261914	CH ₂ CH ₂ CO ₂ H	t-BuOCOCH ₂	C ₃₄ H ₃₇ F ₂ N ₅ O ₉
261915	i-PrO	CH ₂ CO ₂ H	C ₃₀ H ₃₁ F ₂ N ₅ O ₈
261916	CH ₂ CH ₂ CO ₂ Me	3-CO ₂ H-Ph	C ₃₆ H ₃₃ F ₂ N ₅ O ₉

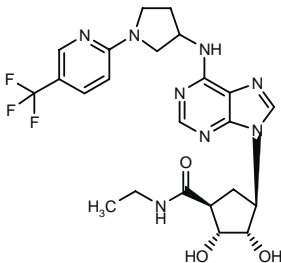
SOURCE – Green Cross (now Yoshitomi).

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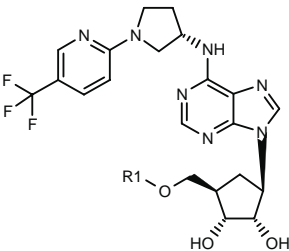
261200

(1*S*,2*R*,3*S*,4*R*)-*N*-Ethyl-2,3-dihydroxy-4-[*N*⁶-[1-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl]adenin-9-yl]-cyclopentane-1-carboxamide



C23-H27-F3-N8-O3; Mol wt: 520.51

ACTION – Metabolically stable adenosine analog with antihypertensive, cardioprotective, antiischemic and antilipolytic properties. Other specifically claimed compounds include the following:



Compound	R2	Formula
261718	H	C ₂₁ H ₂₄ F ₃ N ₇ O ₃
261719	Me	C ₂₂ H ₂₆ F ₃ N ₇ O ₃

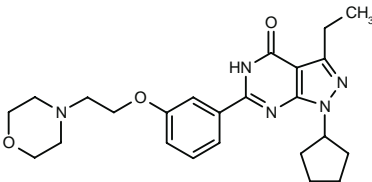
SOURCE – Rhône-Poulenc Rorer.

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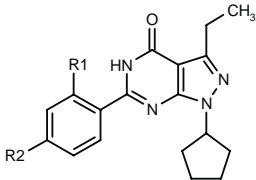
262184

1-Cyclopentyl-3-ethyl-6-[3-[2-(4-morpholinyl)-ethoxy]phenyl]-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



C24-H31-N5-O3; Mol wt: 437.54

ACTION – Agent for the treatment of hypertension and heart failure that acts by inhibition of cGMP phosphodiesterase (PDE V) activity (IC₅₀ = 107 nM). Compound was active in reducing mean arterial pressure in spontaneously hypertensive rats (SHR), giving an ED₂₅ value of 9.5 mg/kg i.v. and a 58% decrease at 30 mg/kg p.o., and it elicited 58% reversal of nitroglycerin-induced tolerance at 0.3 mg/kg i.v. in SHR. Other specifically claimed 6-aryl pyrazolo[3,4-*d*]pyrimidin-4-ones include the following:



Compound	R1	R2	Formula
262381	H	1-imidazolyl	C ₂₁ H ₂₂ N ₆ O
262383	OEt	1-imidazolyl	C ₂₃ H ₂₆ N ₆ O ₂
262384	allyl-O	H	C ₂₁ H ₂₄ N ₄ O ₂

SOURCE – Sanofi.

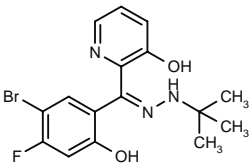
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

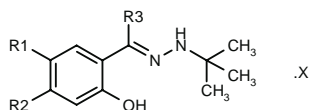
257487

(*Z*)-1-(5-Bromo-4-fluoro-2-hydroxyphenyl)-1-(3-hydroxy-2-pyridyl)methanone *tert*-butylhydrazone



C16-H17-Br-F-N3-O2; Mol wt: 382.23

ACTION – Agent for the treatment of cardiovascular disorders such as hypertension and angina pectoris, a potassium channel opener. Compound was shown to inhibit tetraethylammonium- and barium chloride-induced contractions of rat aorta (100% inhibition at 0.3 μ M), while it exhibited no effect on preparations precontracted with 80 mM KCl. *In vivo*, it increased coronary blood flow by 95% in dogs at 30 μ g administered into the coronary artery, with a $t_{1/2}$ of 78 min. Other compounds from this series of hydrazone derivatives include the following:



Compound	R1	R2	R3	X	Formula
262698	Br	H	1-oxido-3-OH-2-Pyr		C ₁₆ H ₁₈ BrN ₃ O ₃
262699	Br	CN	3-OH-2-Pyr	EtOH .H ₂ O	C ₁₇ H ₁₇ BrN ₄ O ₂ .C ₂ H ₆ O.H ₂ O
262700	Cl	F	3-OH-2-Pyr	H ₂ O	C ₁₆ H ₁₇ ClFN ₃ O ₂ .H ₂ O

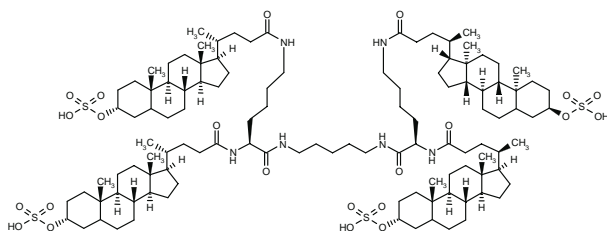
SOURCE – Takeda.

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261523

*N*¹,*N*^{1'}-Pentane-1,5-diylbis[*N*^α,*N*^ε-bis(3 α -sulfooxycholan-24-oyl)lysineamide]



C113-H190-N6-O22-S4; Mol wt: 2113.01

ACTION – Antiproliferative agent, a specifically claimed compound within a series of polysulfolithocolic acid derivatives found to exhibit growth factor receptor-inhibitory activity. It inhibited [¹²⁵I]-VEGF (vascular endothelial growth factor) binding to *flt*-IgG fusion proteins and to human umbilical vein endothelial cells (HUVEC), and it also inhibited VEGF-stimulated HUVEC growth. The compound was effective in a rat model of glucose-induced (diabetic) vascular dysfunction, and it also displayed significant inhibition of serum-stimulated human aortic smooth muscle cell proliferation (63-72% at 30 μ M). Potentially useful in the treatment of diseases characterized by excessive smooth muscle cell proliferation or excessive neovascularization and permeability such as vascular stenosis, postangioplasty restenosis, diabetes, neovascularizing ocular diseases, rheumatoid arthritis and cancer.

SOURCE – Texas Biotechnology.

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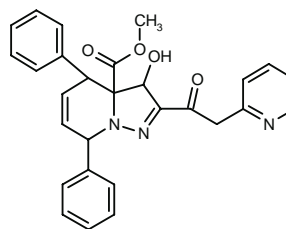
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LJC-11325*

249589

3-Hydroxy-4,7-diphenyl-2-[2-(2-pyridyl)acetyl]-3,3a,4,7-tetrahydropyrazolo[1,5-*a*]pyridine-3a-carboxylic acid methyl ester

7-Hydroxy-2,5-diphenyl-8-[2-(2-pyridyl)acetyl]-1,9-diazabicyclo[4.3.0]nona-3,8-diene-6-carboxylic acid methyl ester



C28-H25-N3-O4; Mol wt: 467.52

ACTION – Cardioprotective agent with both antioxidant effects and the ability to increase myocardial adenosine levels. It improved the decrease in left ventricular developed pressure in isolated perfused rat hearts (3 μ M) subjected to ischemia/reperfusion; it also reduced the incidence of arrhythmia and the decrease in myocardial creatine phosphokinase activity after coronary artery ligation at a dose of 5 mg/kg i.v. In genetically cardiomyopathic hamsters, repeated oral administration of LJC-11325 (30 mg/kg/day for 90 days) inhibited myocardial damage and cardiac hypertrophy. Potentially useful for the treatment of myocardial infarction and heart failure.

SOURCE – Lederle (Japan).

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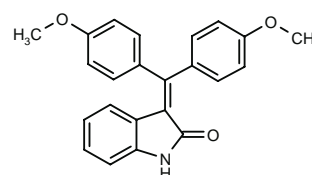
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*Identified compound **249589** (see **249357**) Drug Data Rep 1997, 19(6): 519.

TAS-301*

254185

3-[Bis(4-methoxyphenyl)methylene]indolin-2-one



C23-H19-N-O3; Mol wt: 357.41

ACTION – Agent for the treatment of restenosis that regulates smooth muscle cell (SMC) migration. Compound concentration-dependently inhibited rat SMC migration in response to platelet-derived growth factor (PDGF-BB), as well as the protein tyrosine phosphorylation of focal adhesion kinase (FAK) and paxillin. TAS-301 was found to reduce neointimal formation following carotid artery balloon injury in rats when given at doses of 10-100 mg/kg/day orally for 14 days after denudation, and it significantly reduced migrated SMCs. In a pig model of coronary stenosis, compound was shown to decrease vascular remodeling after angioplasty by inhibiting the contractile action of the adventitia.

SOURCE – Taiho.

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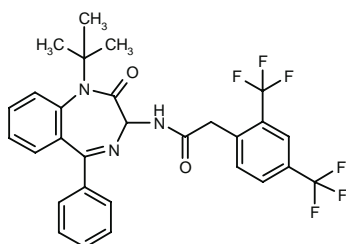
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*Identified compound **254185** Drug Data Rep 1997, 19(11): 989.

ANTIARRHYTHMIC DRUGS

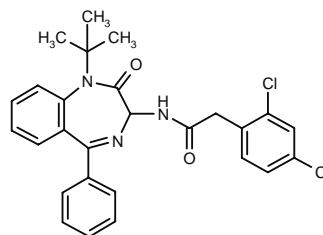
260125

(+)-2-[2,4-Bis(trifluoromethyl)phenyl]-N-(1-*tert*-butyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)-acetamide



C29-H25-F6-N3-O2; Mol wt: 561.53

ACTION – Class III antiarrhythmic agent that is at least 10-fold more potent in blocking $K_{V(s)}$ currents ($IC_{50} < 1 \mu M$ in electrically stimulated guinea pig ventricular myocytes) than $K_{V(n)}$ currents. Another specifically claimed compound from this series of benzodiazepines is:



262705: C27-H25-Cl2-N3-O2: (+)-isomer

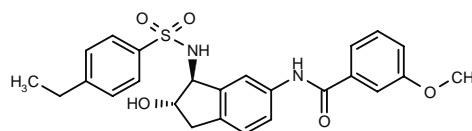
SOURCE – Merck & Co.

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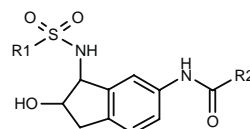
261568

trans-N-[1-(4-Ethylphenyl)sulfonamido]-2-hydroxyindan-6-yl]-3-methoxybenzamide



C25-H26-N2-O5-S; Mol wt: 466.55

ACTION – Agent for the treatment of cardiac arrhythmias and proliferative disorders, a potassium channel blocker with an IC_{50} value of approx. $0.1 \mu M$ when tested *in vitro* for its inhibitory effect on ionic currents through the Kv1.5 channel in CHO cells; it also inhibited human lymphocyte proliferation due to its ability to block the Kv1.3 channel, and was not toxic to these cells after 90-h exposure at $10 \mu M$. It prolonged the action potential by $> 50\%$ in isolated human atrial monocytes at a concentration of $1 \mu M$, and also prolonged the action potential at this concentration in rat cardiac myocytes. A representative compound within a series of voltage-dependent potassium channel blockers, wherein the following are also included:



Compound	R1	R2	Formula
262462	4-Et-Ph	3-Me-Ph	C ₂₅ H ₂₆ N ₂ O ₄ S
262463	4-MeO-Ph	3-MeO-Ph	C ₂₄ H ₂₄ N ₂ O ₆ S
262464	4-Et-Ph	cyclopentyl-CH ₂ CH ₂	C ₂₅ H ₃₂ N ₂ O ₄ S
262465	Ph	3-MeO-Ph	C ₂₃ H ₂₂ N ₂ O ₅ S
262466	4-Et-Ph	bicyclo[2.2.2]-oct-2-yl	C ₂₆ H ₃₂ N ₂ O ₄ S
262467	4-Et-Ph	4-(C ₅ H ₁₁ O)-Ph	C ₂₉ H ₃₄ N ₂ O ₅ S
262468	2-Naph	3-MeO-Ph	C ₂₇ H ₂₄ N ₂ O ₅ S
262469	4-Et-Ph	2-F-Ph	C ₂₄ H ₂₃ FN ₂ O ₄ S

SOURCES – Icagen; Lilly.

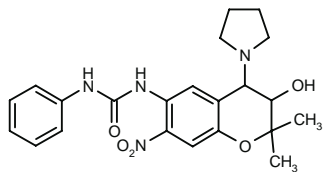
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HEART FAILURE THERAPY

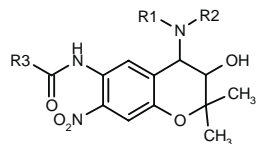
261578

N-[3-Hydroxy-2,2-dimethyl-7-nitro-4-(1-pyrrolidinyl)-3,4-dihydro-2H-1-benzopyran-6-yl]-N'-phenylurea



C22-H26-N4-O5; Mol wt: 426.47

ACTION – Agent for the treatment of cardiac insufficiency that reduces heart muscle energy consumption by reducing heart rate. A negative chronotropic effect was demonstrated in isolated guinea pig hearts, where it produced a concentration-dependent reduction in heart rate: –10.1, –25.6, –65.6 and –87.6%, respectively, at the concentrations of 10, 30, 100 and 300 µM. Other representative compounds within this series of chroman derivatives include the following:



Compound	R1	R2	R3	Formula
262629	-(CH2)4-		CH2Ph	C ₂₃ H ₂₇ N ₃ O ₅
262630	-(CH2)4-		3,4-(MeO)2-PhCH2	C ₂₅ H ₃₁ N ₃ O ₇
262631	Et	H	3,4-(MeO)2-PhCH2	C ₂₃ H ₂₉ N ₃ O ₇
262632	-(CH2)4-		CH2CH2Ph	C ₂₄ H ₂₉ N ₃ O ₅
262633	Et	H	CH2CH2Ph	C ₂₂ H ₂₇ N ₃ O ₅
262634	-(CH2)4-		4-MeO-PhCH2	C ₂₄ H ₂₉ N ₃ O ₆
262635	Et	H	4-MeO-PhCH2	C ₂₂ H ₂₇ N ₃ O ₆
262636	i-Pr	H	3,4-(MeO)2-PhCH2	C ₂₄ H ₃₁ N ₃ O ₇
262637	Et	H	4-MeO-PhCH2CH2	C ₂₃ H ₂₉ N ₃ O ₆
262638	i-Pr	H	4-MeO-PhCH2CH2	C ₂₄ H ₃₁ N ₃ O ₆

SOURCE – Nissan Chem.

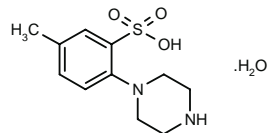
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MCC-135*

168507

5-Methyl-2-(1-piperazinyl)benzenesulfonic acid mono-hydrate



C11-H16-N2-O3-S.H2-O; Mol wt: 274.33

ACTION – Agent for the treatment of cardiovascular disorders such as acute myocardial infarction and heart failure with calcium uptake-enhancing activity. In anesthetized dogs, it showed no inotropic, chronotropic or vasodilating effects at doses of 1-1000 µg/kg i.v. However, it improved regional contractile dysfunction in the posts ischemic stunned myocardium at 3-30 µg/kg i.v. injected 15 min after reperfusion, and it reduced myocardial infarct size in a canine model of sustained left circumflex coronary artery occlusion administered 5 min prior to reperfusion. It was active after chronic oral administration (0.1-1 mg/kg/day x 8 weeks) in preventing the progression of left ventricular (LV) hypertrophy and LV dilatation in rats following myocardial infarction and was also shown to restore depressed LV function in these animals. Compound is being evaluated in phase I clinical trials in Europe for the treatment of heart failure.

SOURCE – Mitsubishi Chem.

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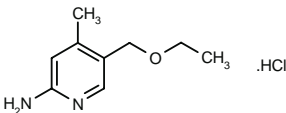
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4. *Mitsubishi Chemical expands R&D at home and abroad.* Prous Science Daily Essentials December 15, 1997.

*Identified compound **168507** (see **166489**) Drug Data Rep 1991, 13(2): 124.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

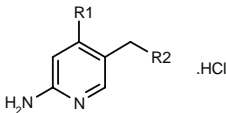
260508

5-(Ethoxymethyl)-4-methylpyridine-2-amine hydrochloride



C9-H14-N2-O.HCl; Mol wt: 202.68

ACTION – Inducible nitric oxide synthase (iNOS) inhibitor (IC₅₀ = 0.39 µM in murine macrophage-derived cells stimulated with lipopolysaccharide), with potential in the treatment of shock, hypotension, arthritis, ischemia and insulin-dependent diabetes. Other related compounds include the following:



Compound	R1	R2	Formula
262266	Me	OMe	C ₈ H ₁₂ N ₂ O.HCl
262267	Me	OCH2CH2OMe	C ₁₀ H ₁₆ N ₂ O ₂ .HCl
262268	H	OEt	C ₈ H ₁₂ N ₂ O.HCl
262269	H	OMe	C ₇ H ₁₀ N ₂ O.HCl
262270	Me	SEt	C ₉ H ₁₄ N ₂ S.HCl

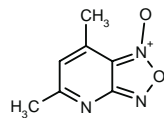
SOURCE – Ono.

REFERENCES

1. Taniguchi, N. et al. (Ono Pharm. Co., Ltd.) *Nitric monoxide synthase inhibitor*. JP 98001470.

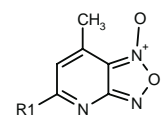
261227

5,7-Dimethyl[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide



C7-H7-N3-O2; Mol wt: 165.15

ACTION – Nitric oxide synthase (NOS) inhibitor with selectivity for the inducible isoform (iNOS; IC₅₀ = 0.84 μM) over the neuronal isoform (nNOS; IC₅₀ = 21 μM) and the endothelial isoform (eNOS; 35% inhibition at 1 mM). Potentially useful for the treatment of septic shock, arthritis, allergic rhinitis, stroke, Parkinson's disease, obesity and pain. Other related compounds include the following:



Compound	R1	Formula
262965	H	C ₈ H ₇ N ₃ O ₂
262966	Pr	C ₉ H ₁₁ N ₃ O ₂

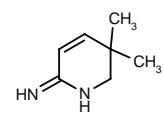
SOURCE – Nippon Kayaku.

REFERENCES

1. Inubushi, A. et al. (Nippon Kayaku Co., Ltd.) *Novel nitrogen monoxide synthase inhibitors*. JP 98081622, WO 9802442.

261852

5,5-Dimethyl-1,2,5,6-tetrahydropyridine-2-imine



C7-H12-N2; Mol wt: 124.19

ACTION – Agent for the treatment or prevention of septic shock, rheumatoid arthritis, ulcerative colitis, insulin-dependent diabetes and tumors, an inducible nitric oxide synthase (iNOS) inhibitor (IC₅₀ = 0.0219 μM in lipopolysaccharide [LPS]-stimulated murine macrophage-derived cells).

SOURCE – Ono.

REFERENCES

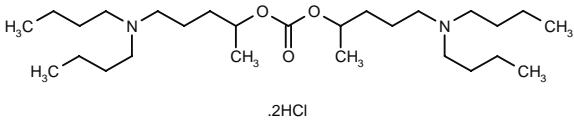
1. Taniguchi, N. et al. (Ono Pharm. Co., Ltd.) *NOS inhibitors*. JP 98036351.

ITF-1779*

262839

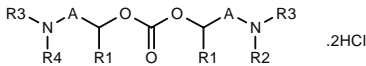
228749 (as hydrate)

Carbonic acid bis[4-(dibutylamino)-1-methylbutyl] diester dihydrochloride



C27-H56-N2-O3.2HCl; Mol wt: 529.67

ACTION – An inhibitor of human tumor necrosis factor-α (huTNF-α) with potential in the treatment of conditions such as sepsis, cachexia, cerebral malaria and rheumatoid arthritis. *In vitro*, it inhibited the cytotoxic activity of different concentrations of huTNF-α on LM cells by 36-78% at 10 μM. It also inhibited IL-6 production induced by IL-1α in LM cells at concentrations of 12.5-100 μM. *In vivo*, it afforded significant protection against lipopolysaccharide (LPS)-induced shock in mice at a dose of 10 mg/kg s.c. Other diaminic carbonates include the following:



Compound	R1	R2	R3=R4	A	Formula
ITF-1493** [230201]	H	i-Pr	i-Pr	-(CH2)3-	C ₂₁ H ₄₄ N ₂ O ₃ .2HCl
ITF-2002*** [230202]	Et	Bu	Bu	-(CH2)3-	C ₂₉ H ₆₀ N ₂ O ₃ .2HCl
ITF-2083 [262841]	Me	Pr	Bu	-(CH2)4-	C ₂₈ H ₅₈ N ₂ O ₃ .2HCl
ITF-2109 [262842]	Me	i-Bu	i-Bu	-(CH2)3-	C ₂₇ H ₅₆ N ₂ O ₃ .2HCl

SOURCE – Italfarmaco.

REFERENCES

1. Sala, A. et al. (Italfarmaco SpA) *Diester of carbonic acid endowed with antiviral and anti-inflammatory activity*. JP 97511497, WO 9523128.

2. Porro, G. et al. *Diaminic carbonates, a new class of anti-inflammatory compounds: Their biological characterization and mode of action*. J Pharmacol Exp Ther 1998, 285(1): 193.

*Identified compound **228749** Drug Data Rep 1996, 18(2): 166.

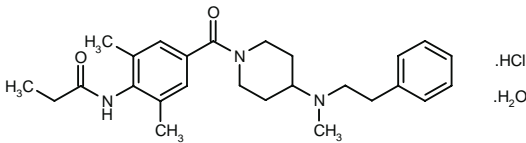
Identified compound **230201 (see **228749**) Drug Data Rep 1996, 18(2): 166.

***Identified compound **230202** (see **228749**) Drug Data Rep 1996, 18(2): 166.

OPC-28326

261725

N-[2,6-Dimethyl-4-[4-[*N*-methyl-*N*-(2-phenylethyl)-amino]piperidin-1-ylcarbonyl]phenyl]propionamide hydrochloride monohydrate



C26-H35-N3-O2.HCl.H2-O; Mol wt: 476.06

ACTION – A selective peripheral vasodilator whose activity appears to involve, in part, α_1 -adrenoceptor blockade. Intraarterial injection of OPC-28326 (0.1-100 nmol) increased blood flow in perfused canine femoral artery preparations, but did not affect coronary artery blood flow, sinoatrial rate or cardiac contractile force in isolated dog heart preparations. In open-chest dogs, the compound (0.1-30 $\mu\text{g/kg}$ i.v.) increased femoral artery blood flow, but only slightly affected coronary, vertebral, renal, carotid and mesenteric artery blood flow, heart rate and cardiac contractile force. It inhibited phenylephrine-induced contractions of dog femoral artery preparations and the phenylephrine-induced pressor response in anesthetized dogs (10-1000 $\mu\text{g/kg}$ i.v.); although it was 300 times less potent than prazosin in the latter test, it was 10 times more potent than prazosin in increasing femoral artery blood flow in open-chest dogs.

SOURCE – Otsuka.

REFERENCES

1. Fujioka, T. et al. (Otsuka Pharm. Co., Ltd.) *Peripheral vasodilating agent containing N-acylated 4-amino piperidine derivs. as active ingredients*. EP 650476, JP 94340627, US 5656642, US 5760058, WO 9422826.

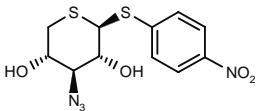
2. Orito, K. et al. *Hemodynamic effects of OPC-28326, a new piperidine derivative, in dogs*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-172.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

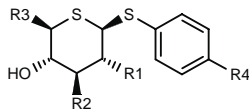
260202

4-Nitrophenyl 3-azido-3-deoxy-1,5-dithio- β -D-xylopyranoside



C11-H12-N4-O4-S2; Mol wt: 328.36

ACTION – Orally active anticoagulant and antithrombotic agent, as demonstrated *in vivo* in a venous thrombosis model in rats (77% inhibition at 12.5 mg/kg p.o.) Other specifically claimed compounds from this series of glycosides include the following:



Compound	R1	R2	R3	R4	Formula
262562	OH	OH	H	C(=NH)SMe	C ₁₃ H ₁₇ NO ₃ S ₃
262563	OH	OH	H	C(=NH)NHNH2	C ₁₂ H ₁₇ N ₃ O ₃ S ₂
262564	OH	N3	H	C(=NH)OMe	C ₁₃ H ₁₆ N ₄ O ₃ S ₂
262565	H	OH	H	CN	C ₁₂ H ₁₃ NO ₂ S ₂
262566	OH	OH	CH2OH	CSNH2	C ₁₃ H ₁₇ NO ₄ S ₃

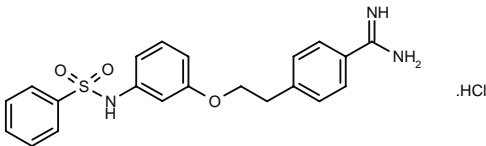
SOURCE – Gedeon Richter.

REFERENCES

1. Kvácsné, Bozó, E. et al. (Richter Gedeon Vegyészeti Gyár RT) *Novel anticoagulant glycosides and pharmaceutical compsns. thereof*. WO 9749716.

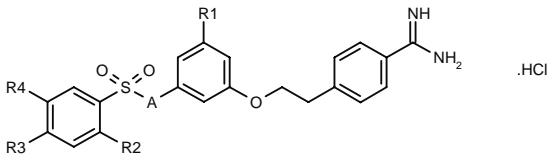
261198

N-[3-[2-(4-Amidinophenyl)ethoxy]phenyl]benzene-sulfonamide hydrochloride



C21-H21-N3-O3-S.HCl; Mol wt: 431.94

ACTION – Anticoagulant and antithrombotic agent with thrombin-inhibitory activity. A representative compound from a series of specifically claimed amidino derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	Formula
262543	Me	H	H	H	O	C ₂₂ H ₂₂ N ₂ O ₄ S.HCl
262544	H	Cl	H	H	NH	C ₂₁ H ₂₀ ClN ₃ O ₃ S.HCl
262545	H	CN	H	H	NH	C ₂₂ H ₂₀ N ₄ O ₃ S.HCl
262546	H	F	H	H	NH	C ₂₁ H ₂₀ FN ₃ O ₃ S.HCl
262547	H	OCF3	H	H	NH	C ₂₂ H ₂₀ F ₃ N ₃ O ₄ S.HCl
262548	H	H	F	H	NH	C ₂₁ H ₂₀ FN ₃ O ₃ S.HCl
262549	H	Me	H	Me	NH	C ₂₃ H ₂₅ N ₃ O ₃ S.HCl

SOURCE – Astra.

REFERENCES

1. Antonsson, T. (Astra AB) *New amidino derivs. and their use as thrombin inhibitors*. WO 9801422.

262181

TF7I-C-[(Gly)₄-Ser]₄-hTFAA

ACTION – Anticoagulant and antithrombotic agent with factor VIIa-inhibitory activity, a fusion protein comprising a factor VIIa active-site inhibitor domain and a tissue factor domain.

SOURCE – Genentech.

REFERENCES

1. Kelley, R.F. et al. (Genentech, Inc.) *Factor VIIa inhibitors*. US 5736364.

ACTION – A selective peripheral vasodilator whose activity appears to involve, in part, α_1 -adrenoceptor blockade. Intraarterial injection of OPC-28326 (0.1-100 nmol) increased blood flow in perfused canine femoral artery preparations, but did not affect coronary artery blood flow, sinoatrial rate or cardiac contractile force in isolated dog heart preparations. In open-chest dogs, the compound (0.1-30 $\mu\text{g/kg}$ i.v.) increased femoral artery blood flow, but only slightly affected coronary, vertebral, renal, carotid and mesenteric artery blood flow, heart rate and cardiac contractile force. It inhibited phenylephrine-induced contractions of dog femoral artery preparations and the phenylephrine-induced pressor response in anesthetized dogs (10-1000 $\mu\text{g/kg}$ i.v.); although it was 300 times less potent than prazosin in the latter test, it was 10 times more potent than prazosin in increasing femoral artery blood flow in open-chest dogs.

SOURCE – Otsuka.

REFERENCES

1. Fujioka, T. et al. (Otsuka Pharm. Co., Ltd.) *Peripheral vasodilating agent containing N-acylated 4-amino piperidine derivs. as active ingredients.* EP 650476, JP 94340627, US 5656642, US 5760058, WO 9422826.

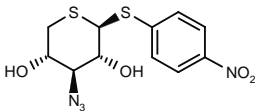
2. Orito, K. et al. *Hemodynamic effects of OPC-28326, a new piperidine derivative, in dogs.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-172.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

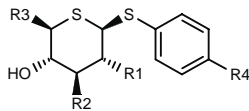
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C11-H12-N4-O4-S2; Mol wt: 328.36

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262564	OH	N3	H	C(=NH)OMe	C ₁₃ H ₁₆ N ₄ O ₃ S ₂
262565	H	OH	H	CN	C ₁₂ H ₁₃ NO ₂ S ₂
262566	OH	OH	CH2OH	CSNH2	C ₁₃ H ₁₇ NO ₄ S ₃

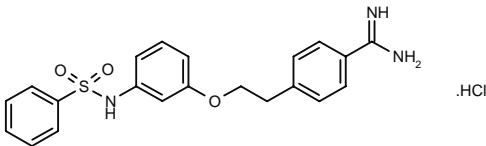
SOURCE – Gedeon Richter.

REFERENCES

1. Kvácsné, Bozó, E. et al. (Richter Gedeon Vegyészeti Gyár RT) *Novel anticoagulant glycosides and pharmaceutical compsns. thereof.* WO 9749716.

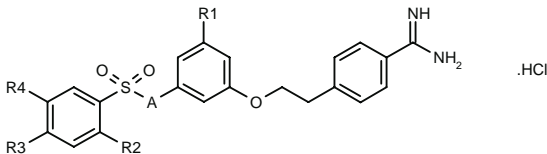
261198

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262544	H	Cl	H	H	NH	C ₂₁ H ₂₀ ClN ₃ O ₃ S.HCl
262545	H	CN	H	H	NH	C ₂₂ H ₂₀ N ₄ O ₃ S.HCl
262546	H	F	H	H	NH	C ₂₁ H ₂₀ FN ₃ O ₃ S.HCl
262547	H	OCF3	H	H	NH	C ₂₂ H ₂₀ F ₃ N ₃ O ₄ S.HCl
262548	H	H	F	H	NH	C ₂₁ H ₂₀ FN ₃ O ₃ S.HCl
262549	H	Me	H	Me	NH	C ₂₃ H ₂₅ N ₃ O ₃ S.HCl

SOURCE – Astra.

REFERENCES

1. Antonsson, T. (Astra AB) *New amidino derivs. and their use as thrombin inhibitors.* WO 9801422.

262181

TF7I-C-[(Gly)₄-Ser]₄-hTFAA

ACTION – Anticoagulant and antithrombotic agent with factor VIIa-inhibitory activity, a fusion protein comprising a factor VIIa active-site inhibitor domain and a tissue factor domain.

SOURCE – Genentech.

REFERENCES

1. Kelley, R.F. et al. (Genentech, Inc.) *Factor VIIa inhibitors.* US 5736364.

DEGR-Factor VIIa

260113

Modified human factor VIIa whose catalytic center is modified by the reaction with dansyl-Glu-Gly-Arg (DEGR) chloromethyl ketone

ACTION – Anticoagulant, a modified factor VIIa that acts as a specific inhibitor of tissue factor/factor VII binding and is thus useful for preventing or treating myocardial injury associated with postischemic reperfusion, for maintaining or improving vascular patency, and for inhibiting thrombus formation. It is expected to be more effective and less likely to cause bleeding complications than heparin when used prophylactically for the prevention of deep vein thrombosis. It blocks thrombin generation, limits platelet deposition and maintains tissue factor-binding activity but lacks factor VIIa enzymatic activity. It inhibited vascular restenosis following balloon angioplasty in atherosclerotic rabbits, as well as tissue factor (TF)- and activated factor VII (FVIIa)-mediated vascular lesion formation induced by mechanical vascular injury in nonhuman primates.

SOURCES – Novo Nordisk; ZymoGenetics.

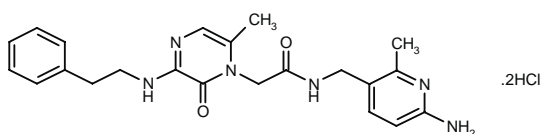
REFERENCES

1. Petersen, L.C. et al. (Novo Nordisk A/S; ZymoGenetics) *Modified factor VII*. WO 9747651.

L-375378*

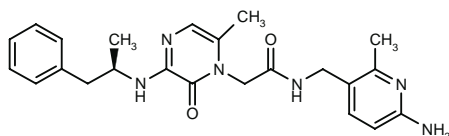
257719

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[6-methyl-2-oxo-3-(2-phenylethylamino)-1,2-dihydropyrazin-1-yl]acetamide dihydrochloride



C22-H26-N6-O2.2HCl; Mol wt: 479.41

ACTION – Highly potent and selective (K_i thrombin = 0.52 nM; K_i trypsin = 1500 nM), orally active thrombin inhibitor selected for clinical development based on its favorable pharmacokinetic profile. Another related pyrazinone acetamide with potent thrombin-inhibitory activity is:



261905: C23-H28-N6-O2

SOURCE – Merck & Co.

REFERENCES

1. Sanderson, P.E. et al. (Merck & Co., Inc.) *Pyrazinone thrombin inhibitors*. WO 9740024.

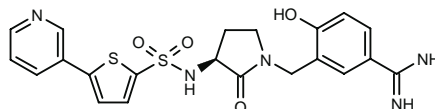
2. Sanderson, P.E.J. *The design of orally active pyridinone and pyrazinone acetamide thrombin inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 199.

*Identified compound **257719** Drug Data Rep 1997, 20(2): 136.

RPR-130737²

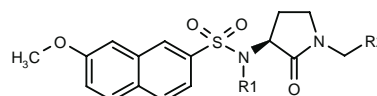
261909

4-Hydroxy-3-[2-oxo-3-(S)-[5-(3-pyridyl)thiophen-2-ylsulfonamido]pyrrolidin-1-ylmethyl]benzamidine



C21-H21-N5-O4-S2; Mol wt: 471.55

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa (K_i = 2 nM) with > 100-fold selectivity over other fibrinolytic proteases. It is reported to be active as an anticoagulant in various *in vivo* models in rats, dogs, and rabbits. Other compounds from this series of sulfonamidopyrrolidinones are:



Compound	R1	R2	Formula
RPR-120844^{1,2} [261910]	Me	5-[NH2C(=NH)]-3-thienyl	C ₂₂ H ₂₄ N ₄ O ₄ S ₂
RPR-130492² [261911]	H	2-OH-5-[NH2C(=NH)]-Ph	C ₂₃ H ₂₄ N ₄ O ₅ S

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

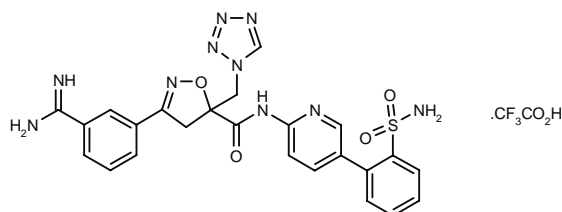
1. Ewing, W.R. et al. (Rhône-Poulenc Rorer Pharm., Inc.) *Substd. (sulfonic acid, sulfonic acid, sulfonylamino or sulfinylamino) N-[(aminoiminomethyl)phenylalkyl]-azaheterocyclyl-amide cpds*. US 5612353, WO 9640679.

2. Ewing, W.R. et al. *Sulfonamidopyrrolidinones: Design, SAR and parenteral activity of a novel class of factor Xa inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 203.

SM-084

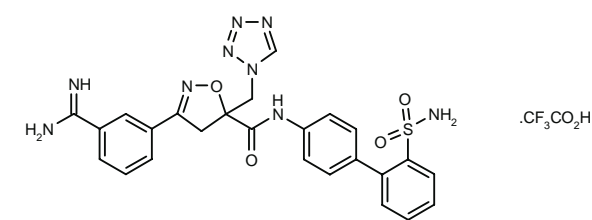
261907

2-[6-[3-(3-Amidinophenyl)-5-(1-tetrazolylmethyl)-4,5-dihydroisoxazol-5-ylcarboxamido]pyridin-3-yl]benzene-sulfonamide trifluoroacetate



C24-H22-N10-O4-S.C2-H-F3-O2; Mol wt: 660.59

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa with subnanomolar affinity and good selectivity over other serine proteases. Compound reportedly exerts potent antithrombotic effects *in vivo* in animal models. Another related isoxazoline derivative is:



SK-549 [261908]: C25-H23-N9-O4-S.C2-H-F3-O2

SOURCE – DuPont Merck.

REFERENCES

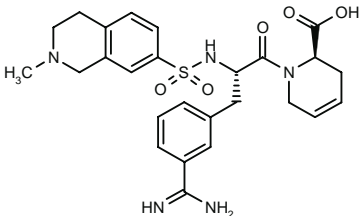
1. Quan, M.L. et al. (The Du Pont Merck Pharm. Co.) *Isoxazoline, isothiazoline and pyrazoline factor Xa inhibitors*. WO 9723212.

2. Quan, M.L. *Design and synthesis of isoxazoline derivatives as factor Xa inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 202.

UK-156406

261906

1-[3-(3-Amidinophenyl)-2(*S*)-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ylsulfonamido)propionyl]-1,2,3,6-tetrahydropyridine-2(*R*)-carboxylic acid



C26-H31-N5-O5-S; Mol wt: 525.62

ACTION – Orally active anticoagulant with potent thrombin-inhibitory activity ($K_i = 0.46$ nM) and selectivity over trypsin ($K_i = 26$ nM). Compound was well tolerated in healthy volunteers administered oral doses of up to 200 mg/kg in phase I clinical trials.

SOURCE – Pfizer.

REFERENCES

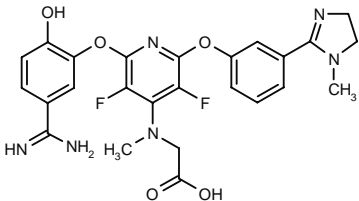
1. Danilewicz, J.C. et al. (Pfizer, Ltd.; Pfizer Res. Dev. Co., NV/SA; Pfizer, Inc.) *Antithrombotic amidinophenylalanine and amidinopyridylalanine derivs*. EP 728132, JP 97500391, US 5750520, WO 9513274.

2. Allen, M. et al. *The discovery of UK-156,406 - An orally active thrombin inhibitor*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 200.

ZK-807191

261986

N-[2-(5-Amidino-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydroimidazol-2-yl)phenoxy]pyridin-4-yl]-*N*-methylglycine



C25-H24-F2-N6-O5; Mol wt: 526.50

ACTION – Anticoagulant and antithrombotic agent, a potent and selective inhibitor of the serine protease factor Xa ($K_i = 0.1$, 2100 and 320 nM, respectively, for factor Xa, thrombin and trypsin). Compound shows a good oral bioavailability and has been selected for clinical evaluation.

SOURCE – Berlex.

REFERENCES

1. Buckman, B.O. et al. (Berlex Labs., Inc.) *Benzamidine derivs. their preparation and their use as anti-coagulants*. EP 813525, US 5691364, WO 9628427.

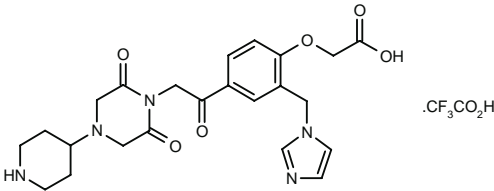
2. Davey, D.D. et al. *Design, synthesis and biological activity of novel factor Xa inhibitors. 5. Optimization of the C-4 position of the 2,6-diphenoxypyridine inhibitors for oral bioavailability*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 125.

3. Shaw, K.J. et al. *Development of potent, selective and orally available factor Xa inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 201.

ANTIPLATELET THERAPY

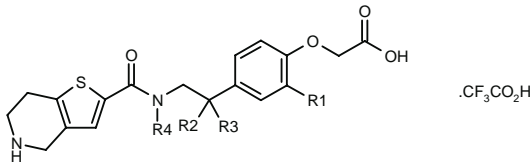
257168

2-[4-[2-[2,6-Dioxo-4-(4-piperidyl)piperazin-1-yl]acetyl]-2-(1-imidazolylmethyl)phenoxy]acetic acid trifluoroacetate

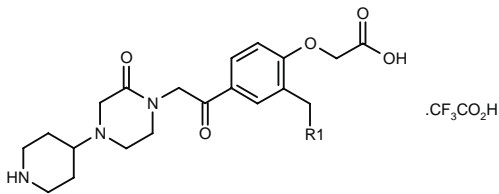


C23-H27-N5-O6.C2-H-F3-O2; Mol wt: 583.52

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist ($IC_{50} = 0.19$ μ M); it inhibited ADP-induced human platelet aggregation with an IC_{50} of 0.031 μ M and human thromboxane synthase with an IC_{50} of 0.69 μ M. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
262410	1-imidazolyl-CH2		-O-	H	C ₂₂ H ₂₂ N ₄ O ₅ S .C ₂ HF ₃ O ₂
262411	3-Pyr-OCH2		-O-	H	C ₂₄ H ₂₃ N ₃ O ₆ S .C ₂ HF ₃ O ₂
262412	OCH2CO2H	H	3-Pyr-O	H	C ₂₅ H ₂₅ N ₃ O ₆ S .C ₂ HF ₃ O ₂
262413	OCH2CO2H	H	3-Pyr-O	Me	C ₂₆ H ₂₇ N ₃ O ₆ S .C ₂ HF ₃ O ₂
262414	H	H	3-Pyr-O	H	C ₂₃ H ₂₃ N ₃ O ₅ S .C ₂ HF ₃ O ₂



Compound	R1	Formula
262415	1-imidazolyl	$\text{C}_{23}\text{H}_{29}\text{N}_5\text{O}_5 \cdot \text{C}_2\text{HF}_3\text{O}_2$
262416	3-Pyr-O	$\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_6 \cdot \text{C}_2\text{HF}_3\text{O}_2$

SOURCE – Meiji Seika.

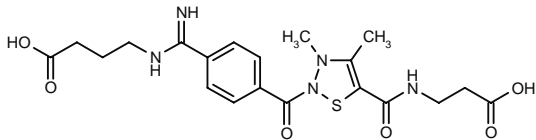
REFERENCES

1. Yamamoto, T. et al. (Meiji Seika Co., Ltd.) *Novel heterocyclic cpds. having platelet aggregation inhibitory effects.* WO 9736887.

TS-943

261727

4-[1-[4-[5-[N-(2-Carboxyethyl)carbamoyl]-3,4-dimethyl-2,3-dihydro-1,2,3-thiadiazol-2-ylcarbonyl]phenyl]-1-aminomethylamino]butyric acid



C20-H25-N5-O6-S; Mol wt: 463.51

ACTION – Antiplatelet and antithrombotic agent, a selective fibrinogen (gpIIb/IIIa) receptor antagonist with an IC_{50} of 29.9 nM for inhibition of [^{125}I]-fibrinogen binding to ADP-activated platelets. Compound possessed higher antiplatelet activity in human compared to animal platelets; in human platelets it inhibited fibrinogen-induced aggregation with an IC_{50} of 7.83 nM and aggregation induced by any agonist with an IC_{50} of 20-40 nM. In guinea pigs, it inhibited platelet aggregation by 80%, prolonged bleeding time to about 5 times the control level and prolonged the time to occlusion in a model of photochemically induced carotid thrombosis at 3 $\mu\text{g}/\text{kg}/\text{min}$.

SOURCE – Taisho.

REFERENCES

1. Goto, J. et al. *Pharmacological profiles of TS-943, a novel platelet gpIIb/IIIa antagonist, in vitro.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-180.

2. Koizumi, C. et al. *Antiplatelet and antithrombotic effects of TS-943, a novel platelet gpIIb/IIIa antagonist, in guinea-pig.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-179.

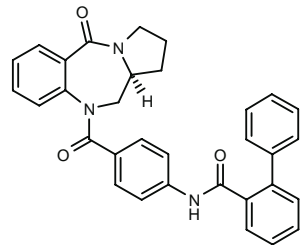
RENAL-UROLOGIC DRUGS

DIURETICS

VP-339

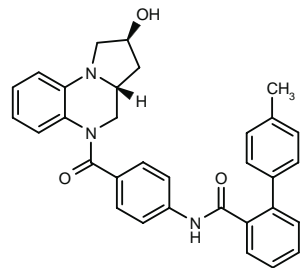
262476

(S)-N-[4-(10-Oxo-2,3,3a,4,5,10-hexahydro-1H-pyrrolo-[1,2-b][2,5]benzodiazepin-5-ylcarbonyl)phenyl]biphenyl-2-carboxamide



C32-H27-N3-O3; Mol wt: 501.58

ACTION – Diuretic, a potent, selective, nonpeptide vasopressin V_2 receptor antagonist ($\text{IC}_{50} = 0.1\text{-}1$ nM) with excellent diuretic effects in rats at 30 mg/kg p.o. Another related compound is:

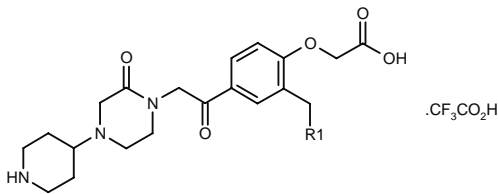


VP-343 [262477]: C32-H29-N3-O3

SOURCE – Wakamoto.

REFERENCES

1. Otake, Y. et al. *Development of novel non-peptide selective vasopressin V_2 receptor antagonist. 1. Synthesis of tri and heterocyclic compounds and structure activity relationship.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)9-40.



Compound	R1	Formula
262415	1-imidazolyl	C ₂₃ H ₂₉ N ₅ O ₅ ·C ₂ HF ₃ O ₂
262416	3-Pyr-O	C ₂₅ H ₃₀ N ₄ O ₆ ·C ₂ HF ₃ O ₂

SOURCE – Meiji Seika.

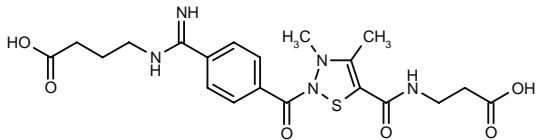
REFERENCES

1. Yamamoto, T. et al. (Meiji Seika Co., Ltd.) *Novel heterocyclic cpds. having platelet aggregation inhibitory effects*. WO 9736887.

TS-943

261727

4-[1-[4-[5-[N-(2-Carboxyethyl)carbamoyl]-3,4-dimethyl-2,3-dihydro-1,2,3-thiadiazol-2-ylcarbonyl]phenyl]-1-aminomethylamino]butyric acid



C20-H25-N5-O6-S; Mol wt: 463.51

ACTION – Antiplatelet and antithrombotic agent, a selective fibrinogen (gpIIb/IIIa) receptor antagonist with an IC₅₀ of 29.9 nM for inhibition of [¹²⁵I]-fibrinogen binding to ADP-activated platelets. Compound possessed higher antiplatelet activity in human compared to animal platelets; in human platelets it inhibited fibrinogen-induced aggregation with an IC₅₀ of 7.83 nM and aggregation induced by any agonist with an IC₅₀ of 20-40 nM. In guinea pigs, it inhibited platelet aggregation by 80%, prolonged bleeding time to about 5 times the control level and prolonged the time to occlusion in a model of photochemically induced carotid thrombosis at 3 µg/kg/min.

SOURCE – Taisho.

REFERENCES

1. Goto, J. et al. *Pharmacological profiles of TS-943, a novel platelet gpIIb/IIIa antagonist, in vitro*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-180.

2. Koizumi, C. et al. *Antiplatelet and antithrombotic effects of TS-943, a novel platelet gpIIb/IIIa antagonist, in guinea-pig*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-179.

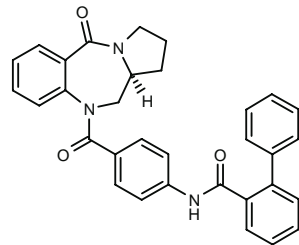
RENAL-UROLOGIC DRUGS

DIURETICS

VP-339

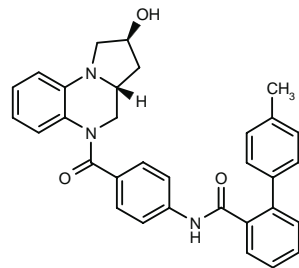
262476

(S)-N-[4-(10-Oxo-2,3,3a,4,5,10-hexahydro-1 H-pyrrolo-[1,2-b][2,5]benzodiazepin-5-ylcarbonyl)phenyl]biphenyl-2-carboxamide



C32-H27-N3-O3; Mol wt: 501.58

ACTION – Diuretic, a potent, selective, nonpeptide vasopressin V₂ receptor antagonist (IC₅₀ = 0.1-1 nM) with excellent diuretic effects in rats at 30 mg/kg p.o. Another related compound is:



VP-343 [262477]: C32-H29-N3-O3

SOURCE – Wakamoto.

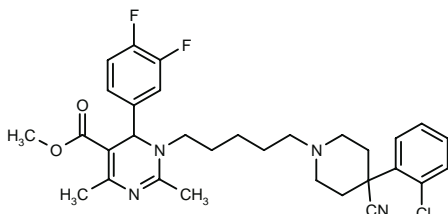
REFERENCES

1. Otake, Y. et al. *Development of novel non-peptide selective vasopressin V2 receptor antagonist. 1. Synthesis of tri and heterocyclic compounds and structure activity relationship*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)9-40.

BENIGN PROSTATIC HYPERPLASIA THERAPY

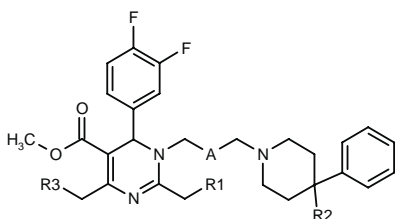
262063

3-[5-[4-(2-Chlorophenyl)-4-cyanopiperidin-1-yl]pentyl]-4-(3,4-difluorophenyl)-2,6-dimethyl-3,4-dihydropyrimidine-5-carboxylic acid methyl ester



C31-H35-Cl-F2-N4-O2; Mol wt: 569.09

ACTION – A potent α_{1A} -adrenoceptor antagonist with a K_i of 0.3 nM using cloned human receptors and selectivity over α_{1B} - (K_i = 149 nM), α_{1D} - (K_i = 293 nM) and α_2 -adrenoceptors, as well as negligible activity at the rat L-type calcium channel. Potentially useful for the symptomatic treatment of benign prostatic hyperplasia. Other compounds within this series of dihydropyrimidines include the following:



Compound	R1	R2	R3	A	Formula
262064	H	Ph	H	-(CH2)3-	C ₃₆ H ₄₁ F ₂ N ₃ O ₂
262065	H	CN	H	(S)-CH2CH2CH(Me)-	C ₃₂ H ₃₈ F ₂ N ₄ O ₂
262066	H	CN	H	(Z)-CH=CHCH2-	C ₃₁ H ₃₄ F ₂ N ₄ O ₂
262067	OMe	CN	H	-(CH2)3-	C ₃₂ H ₃₈ F ₂ N ₄ O ₃
262068	H	CN	OMe	-(CH2)3-	C ₃₂ H ₃₈ F ₂ N ₄ O ₃

SOURCES – Merck & Co.; Synaptic.

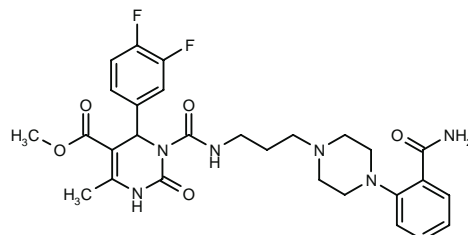
REFERENCES

- Wong, W.C. et al. (Synaptic Pharm. Corp.) *Dihydropyrimidines and uses thereof*. WO 9742956.
- Wong, W.C. et al. *Design and synthesis of dihydropyrimidines as α_{1a} adrenoceptor selective antagonists*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 064.

(+)-SNAP-6543

262062

(+)-3-[N-[3-[4-(2-Carbamoylphenyl)piperazin-1-yl]propyl]carbamoyl]-4-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester



C28-H32-F2-N6-O5; Mol wt: 570.59

ACTION – A potent α_{1A} -adrenoceptor antagonist with a K_i of 0.12 nM using cloned human receptors and selectivity over α_{1B} - (K_i = 187.6 nM), α_{1D} - (K_i = 245.5 nM) and α_2 -adrenoceptors, as well as a number of other receptors and rat L-type calcium channels. Potentially useful for the symptomatic treatment of benign prostatic hyperplasia.

SOURCES – Merck & Co.; Synaptic.

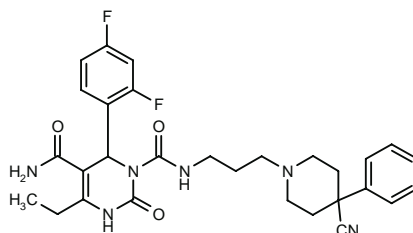
REFERENCES

- Wong, W.C. et al. (Synaptic Pharm. Corp.) *Dihydropyrimidines and uses thereof*. WO 9742956.
- Lagu, B. et al. *Design, synthesis and evaluation of dihydropyrimidinones as alpha 1A selective antagonists: 5. Aryl-piperazine side chains*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 065.

(+)-SNAP-6552

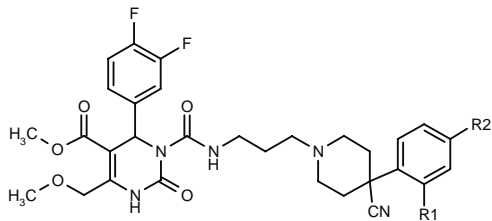
262057

(+)-N³-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]-4-(2,4-difluorophenyl)-6-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-3,5-dicarboxamide



C29-H32-F2-N6-O3; Mol wt: 550.61

ACTION – A potent α_{1A} -adrenoceptor antagonist with a K_i of 0.67 nM using cloned human receptors and selectivity over α_{1B} - (K_i = 782 nM), α_{1D} - (K_i = 1055 nM) and α_2 -adrenoceptors, as well as a number of other receptors and rat L-type calcium channels. Potentially useful for the symptomatic treatment of benign prostatic hyperplasia. Other representative compounds from this series of dihydropyrimidinones include the following:



Compound	R1	R2	Isomer	Formula
(+)-SNAP-6719 [262058]	H	H	(+)	C ₃₀ H ₃₃ F ₂ N ₅ O ₅
SNAP-7493 [262060]	H	F		C ₃₀ H ₃₂ F ₃ N ₅ O ₅
SNAP-7587 [262061]	F	F		C ₃₀ H ₃₁ F ₄ N ₅ O ₅

SOURCES – Merck & Co.; Synaptic.

REFERENCES

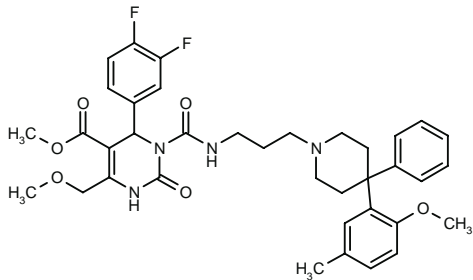
1. Wong, W.C. et al. (Synaptic Pharm. Corp.) *Dihydropyrimidines and uses thereof*. WO 9742956.

2. Nagarathnam, D. et al. *Design, synthesis and evaluation of dihydropyrimidinones as alpha-1A selective antagonists: 6. Synthesis and structure-activity relationship of SNAP 6552 and analogs*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 066.

(+)-SNAP-7242*

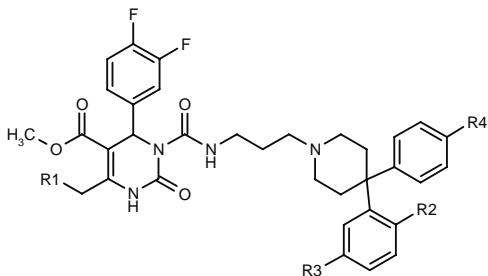
259506

(+)-4-(3,4-Difluorophenyl)-6-(methoxymethyl)-3-[N-[3-[4-(2-methoxy-5-methylphenyl)-4-phenylpiperidin-1-yl]propyl]carbamoyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

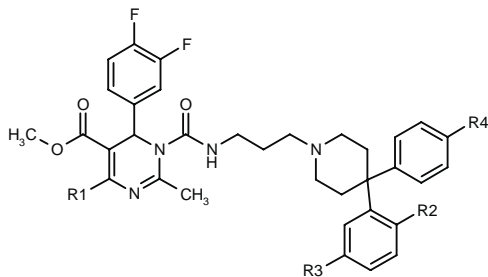


C37-H42-F2-N4-O6; Mol wt: 676.76

ACTION – A potent α_{1A} -adrenoceptor antagonist with a K_i of 0.01 nM using cloned human receptors and selectivity over α_{1B} - (K_i = 13.7 nM) and α_{1D} -adrenoceptors (K_i = 15.4 nM). Potentially useful for the symptomatic treatment of benign prostatic hyperplasia. Other representative compounds from this series include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
(+)-SNAP-7461 [262050]	OMe	OMe	Me	Me	(+)	C ₃₈ H ₄₄ F ₂ N ₄ O ₆
SNAP-7292 [262056]	H	OMe	F	F		C ₃₅ H ₃₆ F ₄ N ₄ O ₅



Compound	R1	R2	R3	R4	Isomer	Formula
(+)-SNAP-7443 [262051]	CH ₂ OMe	Me	H	Me	(+)	C ₃₈ H ₄₄ F ₂ N ₄ O ₄
(+)-SNAP-7555 [262052]	CH ₂ OMe	OMe	Me	Me	(+)	C ₃₈ H ₄₆ F ₂ N ₄ O ₅
(+)-SNAP-7556 [262053]	CH ₂ OMe	Me	F	Me	(+)	C ₃₈ H ₄₃ F ₃ N ₄ O ₄
(-)-SNAP-7180 [262054]	Me	H	H	H	(-)	C ₃₈ H ₃₈ F ₂ N ₄ O ₃
(+)-SNAP-7180 [262055]	Me	H	H	H	(+)	C ₃₈ H ₃₈ F ₂ N ₄ O ₃

SOURCES – Merck & Co.; Synaptic.

REFERENCES

1. Wong, W.C. et al. (Synaptic Pharm. Corp.) *Dihydropyrimidines and uses thereof*. WO 9742956.

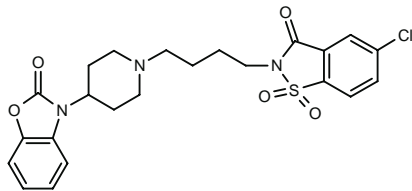
2. Marzabadi, M.R. et al. *Design, synthesis and evaluation of dihydropyrimidinones and dihydropyrimidines as α_{1A} selective antagonists: Modification of the diarylpiperidine moiety*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 067.

*Identified compound **259506** (see **258967**) Drug Data Rep 1998, 20(3): 231.

L-757464

261778

5-Chloro-2-[4-[4-(2-oxo-2,3-dihydrobenzoxazol-3-yl)-piperidin-1-yl]butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide



C23-H24-Cl-N3-O5-S; Mol wt: 489.97

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH), a potent and selective α_{1A} -adrenoceptor antagonist with a K_i of 0.25 nM versus 20 and 322 nM, respectively for α_{1B} - and α_{1D} -adrenoceptors. Compound displayed selectivity for human prostate (K_i = 0.46 nM) compared to human aorta (K_i = 78 nM), and is thus expected to have reduced cardiovascular side effects. It exhibited 28 times greater potency for inhibiting the phenylephrine-induced increase in urethral pressure in dogs compared to the phenylephrine-induced increase in diastolic pressure, and had no effect on blood pressure in various animal models.

SOURCE – Merck & Co.

REFERENCES

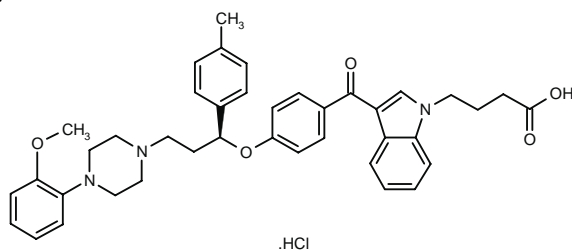
1. Huff, J.R. et al. (Merck & Co., Inc.) α_{1C} Adrenergic receptor antagonists. EP 755392, JP 97512016, US 5760054, WO 9528397.

2. Nerenberg, J.B. et al. *Design and synthesis of N-alkylated saccharins as α_{1A} selective receptor antagonists*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 068.

Z-350

261786

4-[3-[4-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1(S)-(4-methylphenyl)propoxy]benzoyl]-1H-indol-1-yl]butyric acid hydrochloride



C40-H43-N3-O5.HCl; Mol wt: 682.26

ACTION – Agent for the treatment of benign prostatic hyperplasia, a dual α_1 -adrenoceptor antagonist with selectivity for the lower urinary tract ($pIC_{50} = 7.18$ for α_{1A} vs. 6.41 for α_{1B} in binding studies using [3H]-prazosin and rat submaxillary gland [α_{1A}] and liver [α_{1B}] preparations), and steroid 5 α -reductase inhibitor ($IC_{50} = 3.83$ nM using rat prostatic enzyme); it antagonized phenylephrine-induced contractions in rabbit prostate, urethra and aorta with respective pA_2 values of 7.86, 7.51 and 7.13. At doses of 1-10 mg/kg i.d., it demonstrated dose-dependent inhibition of the phenylephrine-induced increase in urethral pressure in rabbits, with weaker effects on mean blood pressure and orthostatic hypotension. It inhibited prostatic steroid 5 α -reductase activity with an ED_{50} of 2.81 mg/kg p.o. in rats and reduced testosterone-induced prostatic growth in castrated rats at 3-30 mg/kg p.o.

SOURCE – Zeria.

REFERENCES

1. Yoshida, K. et al. (Zeria Pharm. Co., Ltd.) *Indole deriv. and medicine containing the same*. EP 753511, US 5760040, WO 9526955.

2. Chikazawa, J. et al. *Development of Z-350, a novel therapeutic agent for urinary disturbance*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XD)11-4.

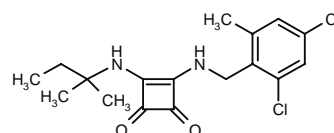
3. Fukuda, Y. et al. *Pharmacological properties of Z-350, which possesses alpha1-adrenoceptor antagonistic and steroid 5alpha-reductase inhibitory actions; (1) in vitro studies*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-439.

4. Fukuta, Y. et al. *Pharmacological properties of Z-350, which possesses alpha1-adrenoceptor antagonistic and steroid 5 alpha-reductase inhibitory actions; (2) in vivo studies*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-440.

TREATMENT OF URINARY INCONTINENCE

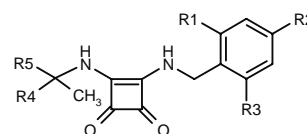
261214

3-(2,4-Dichloro-6-methylbenzylamino)-4-(1,1-dimethylpropylamino)-3-cyclobutene-1,2-dione



C17-H20-Cl2-N2-O2; Mol wt: 355.26

ACTION – Smooth muscle relaxant that acts by activating potassium channels. It inhibited KCl-induced contractions in isolated rat bladder strips with an IC_{50} value of 0.20 ± 0.06 μM . *In vivo*, it produced an $82 \pm 5\%$ reduction in the total number of spontaneous contractions when administered at 3 mg/kg p.o. to female rats with hypertrophied bladders. Potentially useful for the treatment of disorders associated with smooth muscle contraction, particularly urinary incontinence and irritable bowel syndrome. Within this series of specifically claimed derivatives of cyclobutene-3,4-diones, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
261966	H	Cl	Cl	Et	Me	C ₁₆ H ₁₉ Cl ₂ N ₂ O ₂
261967	Me	Cl	Cl	Me	Me	C ₁₆ H ₁₈ Cl ₂ N ₂ O ₂
261968	H	CN	Cl	Me	Me	C ₁₆ H ₁₆ ClN ₃ O ₂
261969	H	CN	Cl	H	t-Bu	C ₁₈ H ₂₀ ClN ₃ O ₂
261970	H	CN	Cl	H	(R)-t-Bu	C ₁₈ H ₂₀ ClN ₃ O ₂
261971	Me	Br	Me	Me	Me	C ₁₇ H ₂₁ BrN ₂ O ₂
261972	H	CN	Cl	Me	Et	C ₁₇ H ₁₈ ClN ₃ O ₂
261973	H	F	H	Et	Me	C ₁₆ H ₁₉ FN ₂ O ₂

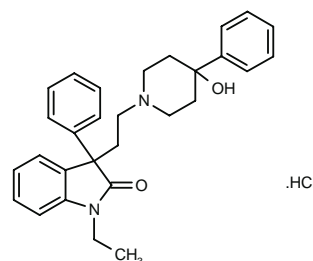
SOURCE – American Home Products.

REFERENCES

1. Antane, M.M. et al. (American Home Prods. Corp.) *Substd. N-arylmethylamino derivs. of cyclobutene-3,4-diones*. WO 9802413.

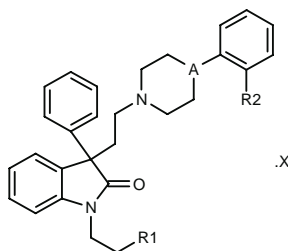
261220

1-Ethyl-3-[2-(4-hydroxy-4-phenylpiperidin-1-yl)ethyl]-3-phenylindolin-2-one hydrochloride

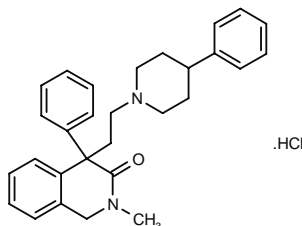


C29-H32-N2-O2.HCl; Mol wt: 477.04

ACTION – Agent for the treatment or prevention of lower urinary tract dysfunction such as urinary incontinence and pollakuria with low toxicity. Compound was shown to inhibit distension-induced rhythmic bladder contractions in anesthetized guinea pigs with a minimum effective dose of 0.001 mg/kg i.v. Compound is also reported to possess analgesic activity. Other related compounds include the following:



Compound	R1	R2	A	X	Formula
261987	H	H	CH	HCl	C ₂₉ H ₃₂ N ₂ O.HCl
261988	Me	OMe	N	2HCl	C ₃₀ H ₃₅ N ₃ O ₂ .2HCl
261989	4-morpholinyl	H	CH	2HCl	C ₃₃ H ₃₉ N ₃ O ₂ .2HCl



261990: C₂₉-H₃₂-N₂-O.HCl

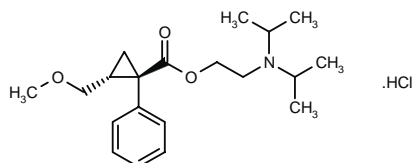
SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chem. Ind., Ltd.) *Bicyclic cpds. for controlling micturition*. WO 9802432.

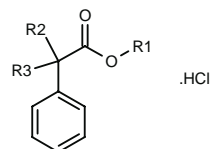
261567

trans-2-(Methoxymethyl)-1-phenylcyclopropanecarboxylic acid 2-(diisopropylamino)ethyl ester hydrochloride



C₂₀-H₃₁-N-O₃.HCl; Mol wt: 369.93

ACTION – Agent for the treatment of urinary incontinence or irritable bowel syndrome that possesses selective antimuscarinic activity on urinary bladder and small intestine muscle. Activity was demonstrated in an *in vitro* functional assay by measuring inhibition of carbachol-induced contractions of isolated guinea pig urinary bladder smooth muscle strips ($K_B = 18$ nM). Its affinity for muscarinic receptors was also determined in binding assays against M_1 receptors (guinea pig cerebral cortex), M_2 receptors (guinea pig heart) and M_3 receptors (guinea pig parotid gland), giving respective K_i values of 5.7, 160 and 99 nM. Other specifically claimed arylcycloalkane carboxylic esters include the following:



Compound	R1	R2,R3	Isomer	X	Formula
262470	CH ₂ CH ₂ N(i-Pr) ₂	-CH ₂ C(Me) ₂ CH ₂ -		HCl	C ₂₁ H ₃₃ NO ₂ .HCl
262471	3-quinuclidinyl	-CH ₂ CH ₂ -		HCl	C ₁₇ H ₂₁ NO ₂ .HCl
262472	CH ₂ CH ₂ N(i-Pr) ₂	-CH(CH ₂ OMe)CH ₂ -	cis	HCl	C ₂₀ H ₃₁ NO ₃ .HCl
262473	CH ₂ CH ₂ N(i-Pr) ₂	-CH ₂ CH(Me)CH ₂ -	cis	HCl	C ₂₀ H ₃₁ NO ₂ .HCl
263231	3-quinuclidinyl	-(CH ₂) ₃ -			C ₁₈ H ₂₃ NO ₂
263232	CH ₂ CH ₂ N(i-Pr) ₂	-(CH ₂) ₅ -			C ₂₁ H ₃₃ NO ₂

SOURCE – Pharmacia & Upjohn.

REFERENCES

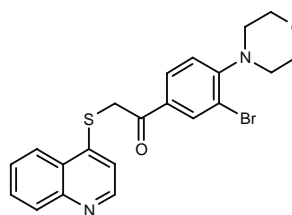
1. Akerblom, E. et al. (Pharmacia & Upjohn AB) *Arylcycloalkane carboxylic esters, their use, pharmaceutical compsns. and preparation*. WO 9804517.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

261572

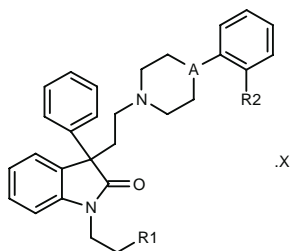
1-[3-Bromo-4-(4-morpholinyl)phenyl]-2-(4-quinolylsulfanyl)ethanone



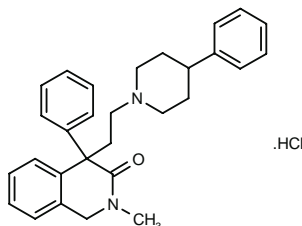
C₂₁-H₁₉-Br-N₂-O₂-S; Mol wt: 443.36

ACTION – Antiulcer agent with potent and selective activity against *Helicobacter pylori* (MIC = 0.0031 µg/ml against *H. pylori* ATCC 43526) and no activity against a broad range of Gram-positive and Gram-negative bacteria (MIC > 100 µg/ml). Other compounds from this series of quinoline sulfide derivatives include the following:

ACTION – Agent for the treatment or prevention of lower urinary tract dysfunction such as urinary incontinence and pollakuria with low toxicity. Compound was shown to inhibit distension-induced rhythmic bladder contractions in anesthetized guinea pigs with a minimum effective dose of 0.001 mg/kg i.v. Compound is also reported to possess analgesic activity. Other related compounds include the following:



Compound	R1	R2	A	X	Formula
261987	H	H	CH	HCl	C ₂₉ H ₃₂ N ₂ O.HCl
261988	Me	OMe	N	2HCl	C ₃₀ H ₃₅ N ₃ O ₂ .2HCl
261989	4-morpholinyl	H	CH	2HCl	C ₃₃ H ₃₉ N ₃ O ₂ .2HCl



261990: C₂₉-H₃₂-N₂-O.HCl

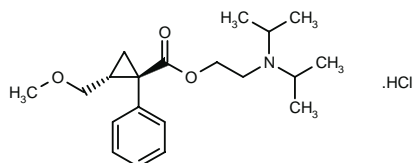
SOURCE – Takeda.

REFERENCES

1. Kato, K. et al. (Takeda Chem. Ind., Ltd.) *Bicyclic cpds. for controlling micturition*. WO 9802432.

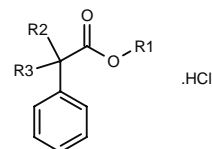
261567

trans-2-(Methoxymethyl)-1-phenylcyclopropanecarboxylic acid 2-(diisopropylamino)ethyl ester hydrochloride



C₂₀-H₃₁-N-O₃.HCl; Mol wt: 369.93

ACTION – Agent for the treatment of urinary incontinence or irritable bowel syndrome that possesses selective antimuscarinic activity on urinary bladder and small intestine muscle. Activity was demonstrated in an *in vitro* functional assay by measuring inhibition of carbachol-induced contractions of isolated guinea pig urinary bladder smooth muscle strips (K_B = 18 nM). Its affinity for muscarinic receptors was also determined in binding assays against M_1 receptors (guinea pig cerebral cortex), M_2 receptors (guinea pig heart) and M_3 receptors (guinea pig parotid gland), giving respective K_i values of 5.7, 160 and 99 nM. Other specifically claimed arylcycloalkane carboxylic esters include the following:



Compound	R1	R2,R3	Isomer	X	Formula
262470	CH ₂ CH ₂ N(i-Pr) ₂	-CH ₂ C(Me) ₂ CH ₂ -		HCl	C ₂₁ H ₃₃ NO ₂ .HCl
262471	3-quinuclidinyl	-CH ₂ CH ₂ -		HCl	C ₁₇ H ₂₁ NO ₂ .HCl
262472	CH ₂ CH ₂ N(i-Pr) ₂	-CH(CH ₂ OMe)CH ₂ -	cis	HCl	C ₂₀ H ₃₁ NO ₃ .HCl
262473	CH ₂ CH ₂ N(i-Pr) ₂	-CH ₂ CH(Me)CH ₂ -	cis	HCl	C ₂₀ H ₃₁ NO ₂ .HCl
263231	3-quinuclidinyl	-(CH ₂) ₃ -			C ₁₈ H ₂₃ NO ₂
263232	CH ₂ CH ₂ N(i-Pr) ₂	-(CH ₂) ₅ -			C ₂₁ H ₃₃ NO ₂

SOURCE – Pharmacia & Upjohn.

REFERENCES

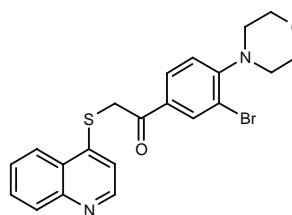
1. Akerblom, E. et al. (Pharmacia & Upjohn AB) *Arylcycloalkane carboxylic esters, their use, pharmaceutical compsns. and preparation*. WO 9804517.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

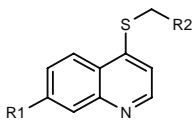
261572

1-[3-Bromo-4-(4-morpholinyl)phenyl]-2-(4-quinolylsulfanyl)ethanone



C₂₁-H₁₉-Br-N₂-O₂-S; Mol wt: 443.36

ACTION – Antiulcer agent with potent and selective activity against *Helicobacter pylori* (MIC = 0.0031 µg/ml against *H. pylori* ATCC 43526) and no activity against a broad range of Gram-positive and Gram-negative bacteria (MIC > 100 µg/ml). Other compounds from this series of quinoline sulfide derivatives include the following:



Compound	R1	R2	Formula
262677	H	4-(PhCH2O)-PhCO	C ₂₄ H ₁₉ N ₂ O ₂ S
262678	H	2-Naph-CO	C ₂₁ H ₁₅ NOS
262679	H	4-t-Bu-PhCO	C ₂₁ H ₂₁ NOS
262680	H	4-(4-morpholinyl)-PhCO	C ₂₁ H ₂₀ N ₂ O ₂ S
262681	H	4-(1-Pip)-PhCO	C ₂₂ H ₂₂ N ₂ OS
262682	H	4-(PhCH2NH)-PhCO	C ₂₄ H ₂₀ N ₂ OS
262683	H	4-N(Me)2-PhCO	C ₁₉ H ₁₈ N ₂ OS
262684	H	4-N(Me)2-PhCH2	C ₁₉ H ₂₀ N ₂ S
262685	SMe	4-N(Me)2-Ph	C ₁₉ H ₂₀ N ₂ S ₂
262686	SMe	4-NH2-Ph	C ₁₇ H ₁₆ N ₂ S ₂
262687	SMe	3-Me-4-(MeNH)-Ph	C ₁₉ H ₂₀ N ₂ S ₂

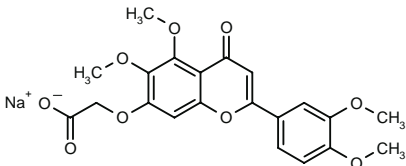
SOURCE – Zenyaku Kogyo.

REFERENCES

1. Kawashima, S. et al. (Zenyaku Kogyo Co., Ltd.) *Quinoline sulfide derivs.* WO 9804529.

261577

2-[2-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-4-oxo-4*H*-1-benzopyran-7-yloxy]acetic acid sodium salt



C21-H19-Na-O9; Mol wt: 438.37

ACTION – Agent for the treatment or prevention of gastrointestinal disorders such as gastritis, ulcers and inflammatory bowel disease. Compound produced 54% inhibition of ethanol/HCl-induced gastric mucosal damage in rats at 0.3 mg/kg p.o., and at 0.3-30 mg/kg p.o. it promoted gastric mucus secretion in rats. Cytoprotective activity was also shown in an acetic acid-induced chronic gastritis model in rats (42% inhibition at 10 mg/kg/day p.o. x 21 days). Compound exhibited antioxidant activity, as demonstrated by inhibition of luminol-dependent chemiluminescence of neutrophils induced by fMLP (IC₅₀ = 1.57 µg/ml). Compound was also found to be effective in a TNBS-induced colitis model in rats at 1 mg/kg p.o. and 0.3 mg/kg rectally, being more potent than mesalazine at 50 mg/kg p.o. LD₅₀ > 5 g/kg p.o. in mice.

SOURCE – Dong A.

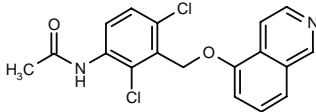
REFERENCES

1. Yoo, M. et al. (Dong A Pharm. Co., Ltd.) *Gastroprotective flavone/flavone cpds. with therapeutic effect on inflammatory bowel disease.* WO 9804541.

FR-180102

262485

N-[2,4-Dichloro-3-(isoquinolin-5-yloxymethyl)phenyl]-acetamide



C18-H14-Cl2-N2-O2; Mol wt: 361.23

ACTION – Highly selective anti-*Helicobacter pylori* agent (MIC = 0.0301 µg/ml) with no activity against other bacteria and thus expected to be free of side effects and drug resistance.

SOURCE – Fujisawa.

REFERENCES

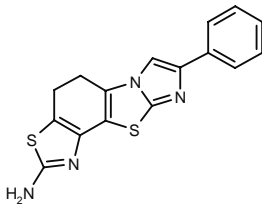
1. Yoshida, Y. et al. *Production of FR180102, a novel benzyloxyisoquinoline derivative, having anti-H. pylori activity.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)9-25.

YJA-20379

261628

8-Phenyl-4,5-dihydroimidazo[2,1-*b*]thiazolo[5,4-*g*]-benzothiazol-2-amine

YJA-20379-1



C16-H12-N4-S2; Mol wt: 324.42

ACTION – Antiulcer agent, a proton pump inhibitor with good inhibitory activity against *Helicobacter pylori* (MIC = 11.7 µg/ml vs. 31.25 µg/ml for omeprazole). Compound was shown to inhibit *H. pylori* urease with an IC₅₀ value of 164 µM vs. 143 µM for omeprazole; however, unlike omeprazole, its inhibitory activity was not affected by acidic conditions. In pharmacokinetic studies in rats, compound exhibited low oral bioavailability at 200 and 500 mg/kg p.o. (6.47% and 4.74% respectively), which appeared to be due to extensive first-pass metabolism rather than poor absorption.

SOURCE – Yung-Jin.

REFERENCES

1. Yoo, H.Y. et al. (Yung-Jin Pharm. Co., Ltd.) *Heterocycle-fused thiazole derivs.* EP 843681, WO 9703076.

2. Kim, S.H. et al. *Determination of a new antiulcer agent, YJA-20379-1 in plasma, urine, blood, and tissue homogenates by high-performance liquid chromatography.* Res Commun Mol Pathol Pharmacol 1997, 97(1): 107.

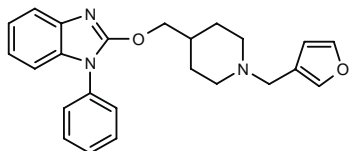
3. Kim, S.H. et al. *Stability, blood partition, and pharmacokinetics of a new reversible proton pump inhibitor, YJA-20379-1.* Res Commun Mol Pathol Pharmacol 1997, 98(1): 77.

4. Woo, T.-W. et al. *Inhibitory action of YJA20379, a new proton pump inhibitor on Helicobacter pylori growth and urease.* Arch Pharm Res 1998, 21(1): 6.

IRRITABLE BOWEL SYNDROME THERAPY

261580

2-[1-(3-Furylmethyl)piperidin-4-ylmethoxy]-1-phenylbenzimidazole



C24-H25-N3-O2; Mol wt: 387.48

ACTION – Agent for the treatment of irritable bowel syndrome, memory disorders, asthma and urinary incontinence with muscarinic M_3 and 5-HT $_4$ receptor-antagonist activity.

SOURCE – Synthélabo.

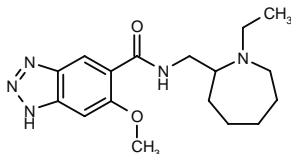
REFERENCES

1. Courtemanche, G. et al. (Synthélabo) *Benzimidazole derivs., preparation thereof, and therapeutical uses thereof.* WO 9804546.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

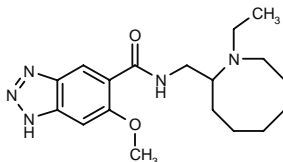
258446

N-(1-Ethylperhydroazepin-2-ylmethyl)-6-methoxybenzotriazole-5-carboxamide



C17-H25-N5-O2; Mol wt: 331.42

ACTION – Gastric prokinetic and antiemetic agent. Another exemplified 6-methoxy-1*H*-benzotriazole-5-carboxamide derivative is:



261343: C18-H27-N5-O2

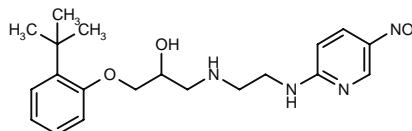
SOURCE – Dainippon.

REFERENCES

1. Kato, S. et al. (Dainippon Pharm. Co., Ltd.) *6-Methoxy-1H-benzotriazole-5-carboxamido cpds.* JP 97301971.

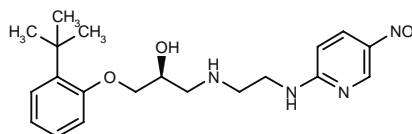
261534

1-(2-*tert*-Butylphenoxy)-3-[2-(5-nitropyridin-2-ylamino)-ethylamino]-2-propanol



C20-H28-N4-O4; Mol wt: 388.47

ACTION – β_3 -Adrenoceptor antagonist with strong affinity for β_3 -adrenoceptors in rat colon but much lower affinity for β_1 - and β_2 -adrenoceptors in guinea pig cardiac and tracheal tissues. Compound is reported to be capable of reversing the inhibitory effects of β -agonists on rat colon motility in the nanomolar range, whereas effects on the other tissues occur in the micromolar range; its β -adrenoceptor-antagonist activity was confirmed *in vivo* in rats by inhibition of the thermogenic effect induced by the β_3 -agonist SR-5861 in brown adipose tissue. Potentially useful in the treatment of gastrointestinal disorders, anxiety, glaucoma, migraine and thyrotoxicosis or hyperparathyroidism, without toxic effects on the cardiovascular or respiratory system. Another specifically claimed phenoxypropanolamine derivative is:



262355: C20-H28-N4-O4

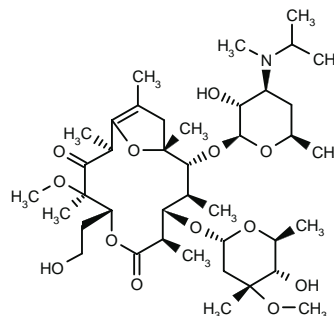
SOURCE – Sanofi.

REFERENCES

1. Badone, D. et al. (Sanofi) *Phenoxypropanolamines having beta3-adrenergic antagonist activity.* WO 9803485.

261553

[2*R*-(2 α ,3 α ,4 α ,5 β ,6 β ,10 β ,12 α ,13 α)]-3-(2,6-Dideoxy-3-*O*,3-*C*-dimethyl- α -L-allopyranosyloxy)-6,9-epoxy-15-hydroxy-12-methoxy-2,4,6,8,10,12-hexamethyl-11-oxo-5-[3,4,6-trideoxy-3-(*N*-isopropyl-*N*-methylamino)- β -D-glucopyranosyloxy]-8-pentadeceno-13-lactone



C40-H69-N-O13; Mol wt: 771.98

ACTION – Gastrointestinal prokinetic agent that displays affinity for the motilin receptor ($IC_{50} = 10$ nM against [^{125}I]-motilin binding to rabbit duodenal preparations), proven to stimulate acetylcholine-induced contractions in isolated rabbit duodenal longitudinal muscle strips ($EC_{50} = 6.61$ nM).

SOURCE – Chugai.

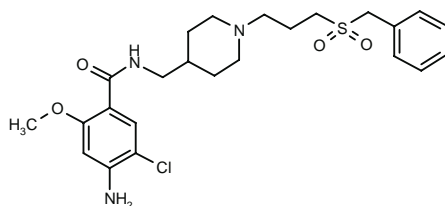
REFERENCES

1. Ishitani, Y. et al. (Chugai Pharm. Co., Ltd.) *Erythromycin derivs.* JP 98087686, WO 9803531.

Y-36912

261788

4-Amino-N-[1-[3-(benzylsulfonyl)propyl]piperidin-4-ylmethyl]-5-chloro-2-methoxybenzamide



C24-H32-Cl-N3-O4-S; Mol wt: 494.05

ACTION – Gastrointestinal motility stimulant, a 5-HT₄ receptor agonist with high binding affinity for the receptor ($K_i = 1.3$ nM) and little or no affinity for 5-HT_{1A}, 5-HT₂, 5-HT₃, dopamine D₁ and D₂, muscarinic and histamine H₁ receptors and α_1 -adrenoceptors. It significantly increased defecation in mice at an oral dose of 0.3 mg/kg and it accelerated colonic transit in guinea pigs at 1 and 3 mg/kg p.o., both effects being inhibited by the selective 5-HT₄ antagonist GR-113808.

SOURCE – Yoshitomi.

REFERENCES

1. Ito, K. et al. (Yoshitomi Pharm. Ind., Ltd.) *Benzoic acid cpds. and medicinal use thereof.* WO 9711054.
2. Sato, N. et al. *Y-36912, a potent and selective 5-HT₄ receptor agonist, enhances lower gastrointestinal motility.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-648.

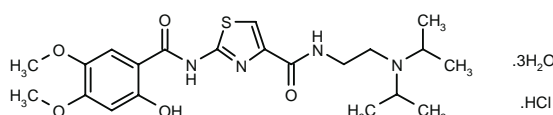
Z-338*

262475

245977 (as anhydrous free base)

N-[4-[N-[2-(Diisopropylamino)ethyl]carbamoyl]thiazol-2-yl]-2-hydroxy-4,5-dimethoxybenzamide hydrochloride trihydrate

N-[2-(Diisopropylamino)ethyl]-2-(2-hydroxy-4,5-dimethoxybenzamido)thiazole-4-carboxamide hydrochloride trihydrate



C21-H30-N4-O5-S.HCl.3H2O; Mol wt: 541.06

ACTION – Gastric prokinetic agent proven to stimulate contractions of isolated guinea pig gastric antrum segments at concentrations > 1 μ M via cholinergic stimulation due to acetylcholine (ACh) release and acetylcholinesterase (AChE) inhibition ($IC_{50} = 3$ μ M against enzyme from human erythrocytes); it exhibited lower affinity for dopamine D₂ receptors compared to other prokinetic agents and showed no affinity for 5-HT₂, 5-HT₃ or 5-HT₄ receptors at 100 μ M. *In vivo*, at doses of 0.3-3 mg/kg i.v. and 3-30 mg/kg p.o., it enhanced gastric motor activity in dogs and improved delayed gastric emptying induced by clonidine in dogs and rats, as well as cholecystokinin-induced delayed gastric emptying in rats, but it did not affect normal gastric emptying or other gastrointestinal functions in rats.

SOURCE – Zeria.

REFERENCES

1. Nagasawa, M. et al. (Zeria Pharm. Co., Ltd.) *Aminothiazole derivs., drug containing the same and intermediate in the production of the cpds.* WO 9636619.
2. Matsunaga, Y. et al. *Z-338, a novel gastroprokinetic agent, stimulates gastrointestinal motor activity and improves delayed gastric emptying in the dog and rat.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-629.
3. Nagasawa, M. et al. *Development of Z-338, a novel drug for improving the digestive motions.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XD)11-5.
5. Ueki, S. et al. *In vitro pharmacological profiles of Z-338, a novel prokinetic agent.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-630.

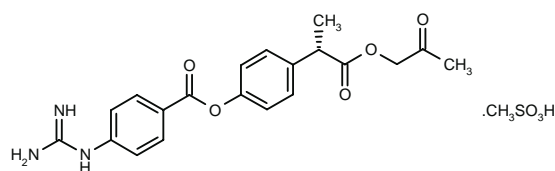
*Identified compound **245977** (see **245405**) Drug Data Rep 1997, 19(4): 339.

TREATMENT OF PANCREATIC DISORDERS

TT-S24

262496

2(S)-[4-(4-Guanidinobenzoyloxy)phenyl]propionic acid 2-oxopropyl ester methanesulfonate



C20-H21-N3-O5.C-H4-O3-S; Mol wt: 479.50

ACTION – Orally active trypsin inhibitor that is at least as effective as camostat in several experimental models of chronic pancreatitis in rats.

SOURCE – Teikoku Chem.

REFERENCES

1. Muramatsu, M. et al. (Teikoku Chem. Ind. Co., Ltd.) *Propionic acid derivs.* EP 673924, JP 94228078, JP 95513988, WO 9413631.
2. Yanagi, T. et al. (Teikoku Chem. Ind. Co., Ltd.) *α -Substd. propionic acid ester derivs.* JP 96020570.
3. Tagami, H. et al. *Effect of methylcarbonylmethyl 2(S)-[4-(4-guanidinobenzoyloxy)phenyl]propionate methanesulfonate (TT-S24) on experimental pancreatitis model.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)9-49.

ENDOCRINE DRUGS

THYROID DISEASE THERAPY

PARICALCITOL

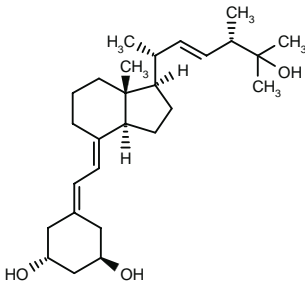
Prop INN

248876

1,25-Dihydroxy-19-norvitamin D₂

(7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol

Paracalcin



C27-H44-O3; Mol wt: 416.64

ACTION – Synthetic vitamin D analog that suppresses parathyroid hormone (PTH) secretion with low calcemic and phosphatemic activity.

INDICATION – Prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure.

PRESENTATION – Single-dose ampules or flip-top vials, 1, 2 and 5 ml containing 5 µg/ml.

PROPRIETARY NAME – *Zemplar* (US).

SOURCE – Abbott.

RECENT REFERENCES

1. DeLuca, H.F. et al. (Wisconsin Alumni Res. Found.) *19-Nor-vitamin D cpds.* US 5587497.

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7. Slatopolsky, E. et al. *Biological activity of 19-nor (19-nor-1,25-(OH)₂D₂): A new vitamin D drug for renal osteodystrophy.* 10th Workshop Vitamin D (May 24-29, Strasbourg) 1997, 215.

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10. Yang, S. et al. *1α,25-Dihydroxyvitamin D₃ and 19-nor-1α,25-dihydroxyvitamin D₂ suppress immunoglobulin production and thymic lymphocyte proliferation in vivo.* Biochem Biophys Acta 1993, 1158(3): 279.

11. *Abbott receives FDA approval for Zemplar™ for suppression of parathyroid hormone in chronic renal failure patients.* Abbott Laboratories Press Release 1998, April 23.

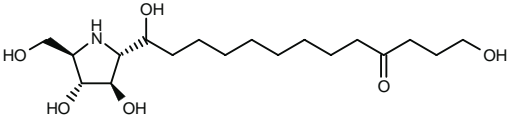
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ANTIDIABETIC DRUGS

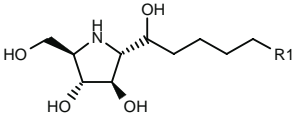
258430

[2*R*-(2α,3β,4α,5β)]-1,13-Dihydroxy-13-[3,4-dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]tridecan-4-one



C18-H35-N-O6; Mol wt: 361.48

ACTION – Antidiabetic and antiobesity agent, an alkaloid isolated from *Broussonia kazinoki* Sieb., with α-glucosidase-, β-glucosidase- and β-galactosidase-inhibitory activity (IC₅₀ = 30, 0.2 and 0.05 µg/ml, respectively). Other related compounds include the following:



Compound	R1	Formula
262706	(CH2)3CO(CH2)4OH	C ₁₈ H ₃₅ NO ₆
262707	2-OH-2-THF-(CH2)6	C ₂₀ H ₃₉ NO ₆
262708	2-OH-2-THP-(CH2)3	C ₁₈ H ₃₅ NO ₆
262709	1,6-dioxaspiro[4.5]decan-7-yl	C ₁₈ H ₃₃ NO ₆
262710	1,6-dioxaspiro[4.5]decan-2-yl	C ₁₈ H ₃₃ NO ₆

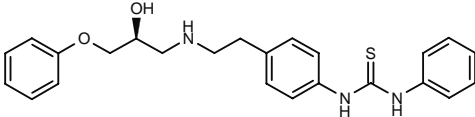
SOURCE – Suntory.

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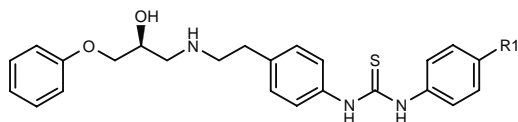
260521

N-[4-[2-[2(*S*)-Hydroxy-3-phenoxypropylamino]ethyl]-phenyl]-*N'*-phenylthiourea



C24-H27-N3-O2-S; Mol wt: 421.56

ACTION – Selective β_3 -adrenoceptor agonist with potential in the treatment of diabetes. Within this series of thiourea derivatives, the following are also included:



Compound	R1	Formula
262271	F	C ₂₄ H ₂₆ FN ₃ O ₂ S
262272	N(Me) ₂	C ₂₆ H ₃₂ N ₄ O ₂ S

SOURCE – Yamanouchi.

REFERENCES

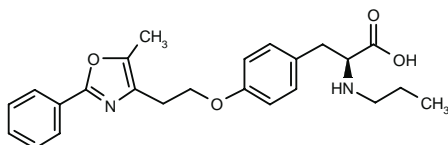
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HQL-975

246871

4-O-[2-(5-Methyl-2-phenyloxazol-4-yl)ethyl]-N-propyl-L-tyrosine

3-[4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]-2(S)-(propylamino)propionic acid



C₂₄H₂₈N₂O₄; Mol wt: 408.50

ACTION – Orally active antidiabetic agent thought to act as an insulin sensitizer. In db/db mice, a genetically obese non-insulin-dependent diabetes mellitus (NIDDM) model, title compound at doses of 3.7-34.1 mg/kg/day x 7 days administered in the diet improved both nonfasting and fasting hyperglycemia and glucose tolerance. It appears to increase hepatic glucose utilization and decrease hepatic glucose production. The LD₅₀ was > 2000 mg/kg p.o. in both male and female mice and no general pharmacological effects were observed in male mice treated orally at a dose of 1000 mg/kg/day for 7 days.

SOURCE – Sumitomo Metal.

REFERENCES

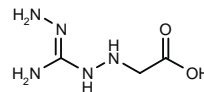
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PNU-106817

261730

2-(N²-Aminoguanidin-N¹-ylamino)acetic acid

N-(N²-Aminoguanidin-N¹-yl)glycine



C₃H₉N₅O₂; Mol wt: 147.14

ACTION – Aminoguanidine antidiabetic agent with more potent antihyperglycemic activity than previous lead compounds; it is not a substrate for creatine transport or creatine kinase. Currently being evaluated as a clinical candidate.

SOURCE – Pharmacia & Upjohn.

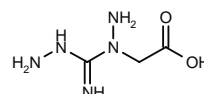
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PNU-140975*

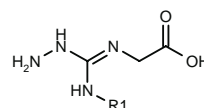
238831

2-(1,3-Diaminoguanidino)acetic acid



C₃H₉N₅O₂; Mol wt: 147.14

ACTION – Antidiabetic agent selected for further development from a series of amino- and diaminoguanidines related to PNU-99022. It proved effective in reducing blood glucose levels in insulin-resistant hyperglycemic, hyperinsulinemic, obese KKA^Y mice (500 mg/kg in the diet), and it decreased blood glucose levels and induced weight loss selectively from fat body mass in C57Bl6^{Job/ob} mice (50 mg/kg day in the diet). In addition, PNU-140975 was effective in reducing both glucose and insulin plasma levels in insulin-resistant rhesus monkeys (3 or 10 mg/kg/day p.o.). Other related compounds are:



Compound	R1	Formula
PNU-106435** [238443]	NH ₂	C ₃ H ₉ N ₅ O ₂
PNU-105126*** [238828]	H	C ₃ H ₈ N ₄ O ₂

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Larsen, S.D. et al. (The Upjohn Co.) *Aminoguanidine carboxylates for the treatment of non-insulin-dependent diabetes mellitus*. WO 9616031.

2. Stevens, F.C. et al. *Development of amino- and diaminoguanidine antidiabetic agents*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 047.

*Identified compound **238831** (see **238443**) Drug Data Rep 1996, 18(9): 810.

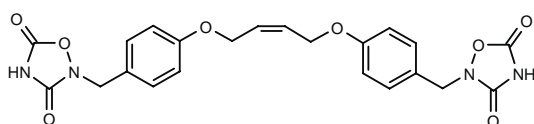
Identified compound **238443 Drug Data Rep 1996, 18(9): 810.

***Identified compound **238828** (see **238443**) Drug Data Rep 1996, 18(9): 810.

YM-440

259652

2,2'-[2-(Z)-Butene-1,4-diyl]dioxymbis(1,4-phenylene)-bis(methylene)bis[1,2,4-oxadiazole-3,5(2H,4H)-dione]



C22-H20-N4-O8; Mol wt: 468.42

ACTION – Antidiabetic agent proven effective in animal models of non-insulin-dependent diabetes mellitus (NIDDM). It displayed more potent hypoglycemic activity than troglitazone *in vivo* in kk and ob/ob mice (ED_{30} = 26 and 3.6 mg/kg p.o., respectively). It enhanced 2-deoxyglucose uptake in adipocytes (179% of basal uptake at 10 μ M) but showed little or no PPAR γ -agonist activity in CV-1 cells, suggesting that its principal mechanism of action may be different from the thiazolidinediones. Currently in phase I trials.

SOURCE – Yamanouchi.

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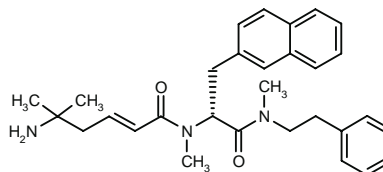
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

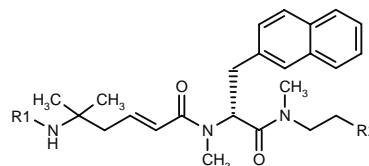
261532

2-(R)-[5-Amino-5,N-dimethyl-2(E)-hexenamido]-N-methyl-3-(2-naphthyl)-N-(2-phenylethyl)propionamide

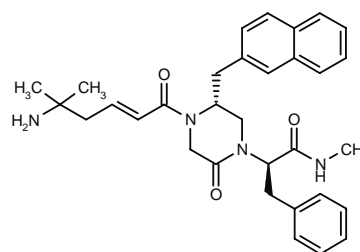


C30-H37-N3-O2; Mol wt: 471.64

ACTION – Agent with growth hormone-releasing activity able to stimulate the release of growth hormone from the pituitary and claimed to be suitable for oral, nasal, transdermal, pulmonary or parenteral administration. Other related compounds include the following:



Compound	R1	R2	Formula
263023	(R)-CH ₂ CH(OH)Me	Ph	C ₃₃ H ₄₃ N ₃ O ₃
263024	H	2-thienyl	C ₂₈ H ₃₅ N ₃ O ₂ S
263025	Me	2-thienyl	C ₂₉ H ₃₇ N ₃ O ₂ S
263026	H	CH ₂ Ph	C ₃₁ H ₃₉ N ₃ O ₂
263027	Me	Ph	C ₃₁ H ₃₉ N ₃ O ₂



263028: C32-H38-N4-O3

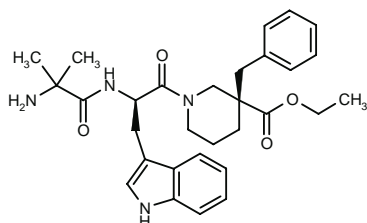
SOURCE – Novo Nordisk.

REFERENCES

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L-163540***261780****228047** (as hydrochloride)

1-[2(*R*)-(2-Amino-2-methylpropionamido)-3-(3-indolyl)propionyl]-3(*S*)-benzylpiperidine-3-carboxylic acid ethyl ester



C30-H38-N4-O4; Mol wt: 518.65

ACTION – Potent, orally bioavailable growth hormone (GH) secretagogue proven active both *in vitro* in the rat pituitary cell assay ($EC_{50} = 1.6$ nM) and *in vivo* by pulsatile increases in GH in dogs at oral doses as low as 0.25 mg/kg.

SOURCE – Merck & Co.

REFERENCES

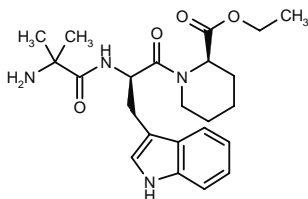
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2. Yang, L. et al. *L-163,540, a potent and orally bioavailable short duration growth hormone secretagogue*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 020.

*Identified compound **228047** (see **226190**) Drug Data Rep 1995, 17(11): 1018.

L-164013***262284****226190** (as hydrochloride)

1-[2(*R*)-(2-Amino-2-methylpropionamido)-3-(1*H*-indol-3-yl)propionyl]piperidine-2(*R*)-carboxylic acid ethyl ester



C23-H32-N4-O4; 428.53

ACTION – Growth hormone (GH) secretagogue shown to stimulate the release of GH with an ED_{50} of 6 nM in the rat pituitary assay and to be orally active in dogs at a dose of 0.5 mg/kg.

SOURCE – Merck & Co.

REFERENCES

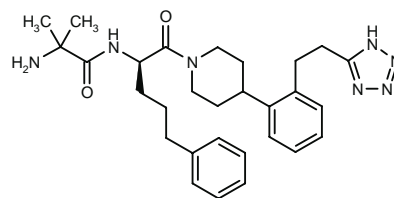
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2. Morriello, G. et al. *Pipecolic acid derivatives as novel growth hormone secretagogues*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 059.

*Identified compound **226190** Drug Data Rep 1995, 17(11): 1018.

L-165034**261779**

2-Amino-2-methyl-*N*-[4-phenyl-1(*R*)-[4-[2-[2-(1*H*-tetrazol-5-yl)ethyl]phenyl]piperidin-1-ylcarbonyl]butyl]-propionamide



C29-H39-N7-O2; Mol wt: 517.67

ACTION – Potent growth hormone (GH) secretagogue, the best compound from a series of peptidomimetic phenyl piperidine-based compounds with an EC_{50} of 0.090 nM in the *in vitro* rat pituitary cell GH release assay; also active *in vivo* in pigs at concentrations of 0.3 µg/kg i.v. and 0.3-3 µg/kg p.o.

SOURCE – Merck & Co.

REFERENCES

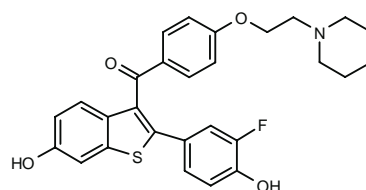
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TREATMENT OF GYNECOLOGICAL DISORDERS

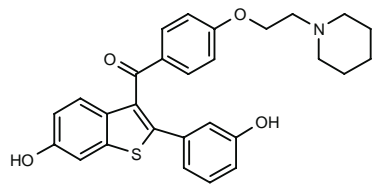
262102

1-[2-(3-Fluoro-4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl]-1-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone



C28-H26-F-N-O4-S; Mol wt: 491.58

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders related to hyperlipidemia and estrogen-dependent cancers, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, compound was shown to significantly decrease cholesterol levels at 0.01-10 mg/kg/day p.o. x 4 days, while increasing uterine weight to a lesser extent than 17α-ethinylestradiol at 0.1 mg/kg/day p.o. x 4 days; at these doses, compound was shown to produce much lower increases in uterus eosinophil infiltration than 17α-ethinylestradiol. It also prevented bone loss in a dose-dependent manner in ovariectomized rats and was found to inhibit the proliferation of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 0.3 nM. Another related benzothiophene derivative is:



262942: C28-H27-N-O4-S

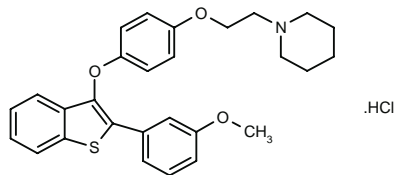
SOURCE – Lilly.

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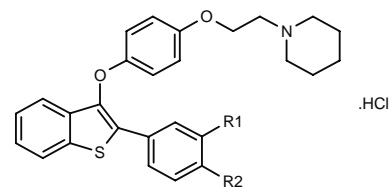
262112

2-(3-Methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]benzo[b]thiophene hydrochloride



C28-H29-N-O3-S.HCl; Mol wt: 496.06

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders related to hyperlipidemia and estrogen-dependent cancers, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, it reduced serum cholesterol levels (55.6% at 0.1 mg/kg/day p.o.) with little stimulatory effect on the uterus and no stimulatory effect on eosinophil infiltration into the uterus, contrary to the effects observed with 17α-ethinylestradiol at the same dose. Within this series of benzothiophene derivatives, the following are also included:



Compound	R1	R2	Formula
262940	OH	H	C ₂₇ H ₂₇ NO ₃ S.HCl
262941	F	OMe	C ₂₈ H ₂₈ FNO ₃ S.HCl

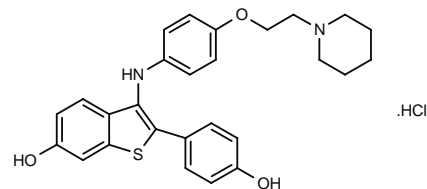
SOURCE – Lilly.

REFERENCES

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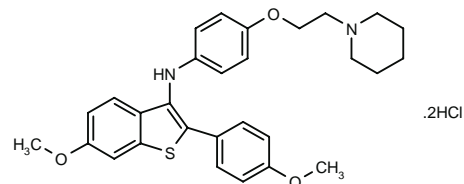
262122

N-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amine hydrochloride



C27-H28-N2-O3-S.HCl; Mol wt: 497.05

ACTION – Agent for the treatment of postmenopausal syndrome including osteoporosis, hyperlipidemia, breast and uterine cancer, and also for the treatment of uterine fibroid disease, endometriosis and aortic smooth muscle cell proliferation. At a dose of 0.1 mg/kg/day p.o. x 4 days the compound produced a significant decrease in serum cholesterol but a substantially lower increase in uterine weight as compared to 17α-ethinylestradiol in ovariectomized rats. It also prevented bone loss in a dose-dependent manner in ovariectomized rats. Another compound from this series of benzothiophenes is:



262964: C29-H32-N2-O3-S.2HCl

SOURCE – Lilly.

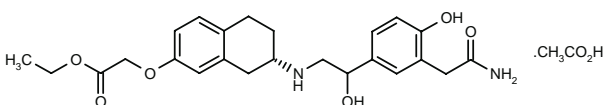
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**UTERINE STIMULANTS
AND TOCOLYTICS**

259207

2-[7(S)-[2-[3-(Carbamoylmethyl)-4-hydroxyphenyl]-2-hydroxyethylamino]-5,6,7,8-tetrahydro-2-naphthoxy]acetic acid ethyl ester acetate



C24-H30-N2-O6.C2-H4-O2; Mol wt: 502.56

ACTION – Potent and selective β_2 -adrenoceptor agonist (EC_{50} = 18 nM for inducing contractions in isolated pregnant rat uterus) with much weaker β_1 -adrenoceptor-agonist activity (EC_{20} = 100 μ M for increase in heart rate in isolated rat atrium). Potentially useful for preventing abortion and premature delivery and also as a bronchodilator.

SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharm. Co., Ltd.) *3,4-Disubst.-phenylethanol-aminotetraline derivs.* JP 97328459.

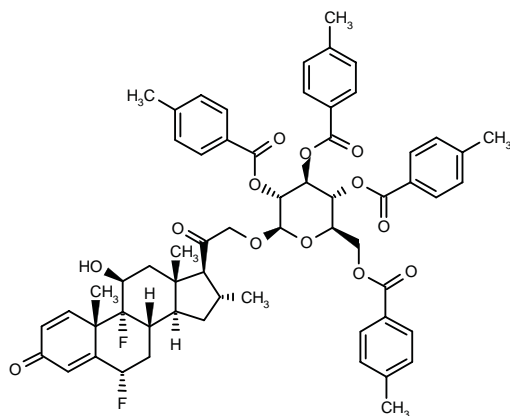
DERMATOLOGIC DRUGS

TOPICAL CORTICOSTEROIDS

NM-135

261595

(6 α ,11 β ,16 α)-6,9-Difluoro-11-hydroxy-16-methyl-21-[2,3,4,6-tetra-*O*-(4-methylbenzoyl)- β -D-glucopyranosyl-oxy]pregna-1,4-diene-3,20-dione



C60-H62-F2-O13; Mol wt: 1029.14

ACTION – Glucocorticoid with potent local anti-inflammatory activity and reduced systemic side effects, proven effective in the croton oil-induced ear edema and granuloma pouch models and the paper disk granuloma model in rats; it was as effective as betamethasone 17-valerate, whereas no systemic side effects such as atrophy of the thymus and adrenals were observed even at higher doses.

SOURCES – MECT; Nisshin Food Products.

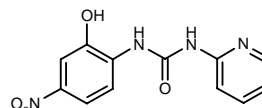
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ANTIPSORIATICS

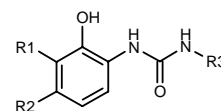
260154

N-(2-Hydroxy-4-nitrophenyl)-*N'*-(2-pyridyl)urea



C12-H10-N4-O4; Mol wt: 274.24

ACTION – IL-8 receptor antagonist with potential in the treatment of a broad range of IL-8-mediated diseases such as psoriasis, arthritis, asthma, inflammatory bowel disease, stroke, septic shock, thrombosis, graft-versus-host disease, Alzheimer's disease and angiogenesis. It is capable of inhibiting the binding of a chemokine such as IL-8, GRO α , GRO β , GRO γ , ENA-78 or NAP-2, particularly IL-8, to the IL-8 α or β receptor (now known as CXCR1 and CXCR2, respectively), and thereby inhibit cytokine function. Other compounds from this series of urea derivatives include the following:



Compound	R1	R2	R3	Formula
262649	H	NO2	3-Pyr	C ₁₂ H ₁₀ N ₄ O ₄
262650	H	NO2	4-Pyr	C ₁₂ H ₁₀ N ₄ O ₄
262651	CN	H	2-Cl-3-Pyr	C ₁₃ H ₉ ClN ₄ O ₂

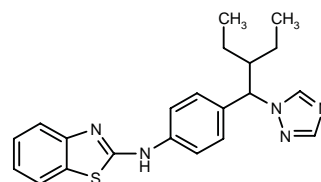
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists.* WO 9749399.

260194

(\pm)-*N*-(2-Benzothiazolyl)-*N*-[4-[2-ethyl-1-(1,2,4-triazol-1-yl)butyl]phenyl]amine



C21-H23-N5-S; Mol wt: 377.51

ACTION – Retinoid mimetic that suppresses the plasma elimination of retinoic acid, potentially useful for the treatment of keratinization disorders such as psoriasis, as well as for the treatment of cancer. *In vitro*, it inhibited retinoic acid metabolism in human breast cancer MCF-7 cells with an IC_{50} < 10 nM. *In vivo*, it was shown to suppress estradiol undecylate-induced vaginal keratinization in ovariectomized rats, with a lowest active dose (LAD; dose at which 50% of animals show complete suppression) of 2.5 mg/kg p.o. or less. Other specifically claimed compounds from this series of heteroarylamines include the following:

ACTION – Potent and selective β_2 -adrenoceptor agonist (EC_{50} = 18 nM for inducing contractions in isolated pregnant rat uterus) with much weaker β_1 -adrenoceptor-agonist activity (EC_{20} = 100 μ M for increase in heart rate in isolated rat atrium). Potentially useful for preventing abortion and premature delivery and also as a bronchodilator.

SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharm. Co., Ltd.) *3,4-Disubst.-phenylethanol-aminotetraline derivs.* JP 97328459.

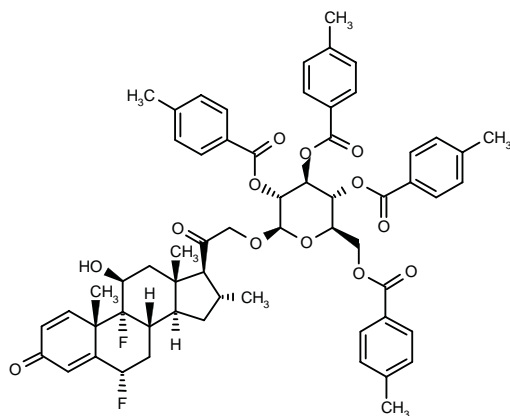
DERMATOLOGIC DRUGS

TOPICAL CORTICOSTEROIDS

NM-135

261595

(6 α ,11 β ,16 α)-6,9-Difluoro-11-hydroxy-16-methyl-21-[2,3,4,6-tetra-*O*-(4-methylbenzoyl)- β -D-glucopyranosyl-oxy]pregna-1,4-diene-3,20-dione



C60-H62-F2-O13; Mol wt: 1029.14

ACTION – Glucocorticoid with potent local anti-inflammatory activity and reduced systemic side effects, proven effective in the croton oil-induced ear edema and granuloma pouch models and the paper disk granuloma model in rats; it was as effective as betamethasone 17-valerate, whereas no systemic side effects such as atrophy of the thymus and adrenals were observed even at higher doses.

SOURCES – MECT; Nisshin Food Products.

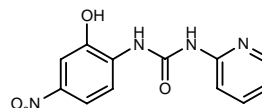
REFERENCES

1. Sugai, K. et al. (MECT Corp.) *21-Subst. steroid cpd.* EP 721956, JP 96510218, WO 9509177.
2. Ishii, T. et al. *Local anti-inflammatory activity and its dissociation from systemic side effects of NM-135, a new topical glucocorticoid.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-136.

ANTIPSORIATICS

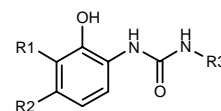
260154

N-(2-Hydroxy-4-nitrophenyl)-*N'*-(2-pyridyl)urea



C12-H10-N4-O4; Mol wt: 274.24

ACTION – IL-8 receptor antagonist with potential in the treatment of a broad range of IL-8-mediated diseases such as psoriasis, arthritis, asthma, inflammatory bowel disease, stroke, septic shock, thrombosis, graft-versus-host disease, Alzheimer's disease and angiogenesis. It is capable of inhibiting the binding of a chemokine such as IL-8, GRO α , GRO β , GRO γ , ENA-78 or NAP-2, particularly IL-8, to the IL-8 α or β receptor (now known as CXCR1 and CXCR2, respectively), and thereby inhibit cytokine function. Other compounds from this series of urea derivatives include the following:



Compound	R1	R2	R3	Formula
262649	H	NO2	3-Pyr	C ₁₂ H ₁₀ N ₄ O ₄
262650	H	NO2	4-Pyr	C ₁₂ H ₁₀ N ₄ O ₄
262651	CN	H	2-Cl-3-Pyr	C ₁₃ H ₉ ClN ₄ O ₂

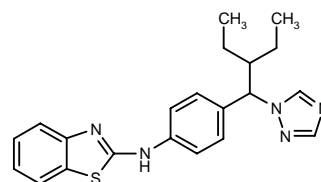
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists.* WO 9749399.

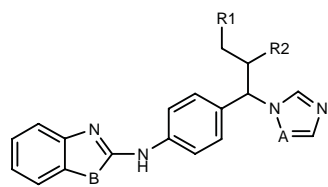
260194

(\pm)-*N*-(2-Benzothiazolyl)-*N*-[4-[2-ethyl-1-(1,2,4-triazol-1-yl)butyl]phenyl]amine



C21-H23-N5-S; Mol wt: 377.51

ACTION – Retinoid mimetic that suppresses the plasma elimination of retinoic acid, potentially useful for the treatment of keratinization disorders such as psoriasis, as well as for the treatment of cancer. *In vitro*, it inhibited retinoic acid metabolism in human breast cancer MCF-7 cells with an IC_{50} < 10 nM. *In vivo*, it was shown to suppress estradiol undecylate-induced vaginal keratinization in ovariectomized rats, with a lowest active dose (LAD; dose at which 50% of animals show complete suppression) of 2.5 mg/kg p.o. or less. Other specifically claimed compounds from this series of heteroarylamines include the following:



Compound	R1	R2	A	B	Formula
262557	H	N(Me)2	CH	S	C ₂₁ H ₂₃ N ₅ S
262558	H	N(Me)2	CH	S	C ₂₁ H ₂₃ N ₅ S
262559	H	N(Me)2	CH	S	C ₂₁ H ₂₃ N ₅ S
262560	Me	Et	N	S	C ₂₁ H ₂₃ N ₅ S
262561	Me	Et	N	O	C ₂₁ H ₂₃ N ₅ O

SOURCE – Janssen.

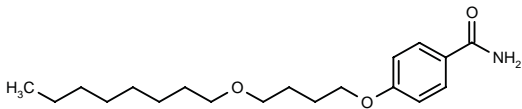
REFERENCES

1. Venet, M.G. et al. (Janssen Pharm. NV) *N*-[4-(Heteroaryl)methyl]phenyl]-heteroarylamines. WO 9749704.

ACNE THERAPY

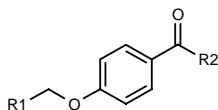
259202

4-(4-Octyloxybutoxy)benzamide



C19-H31-N-O3; Mol wt: 321.46

ACTION – Antiacne agent, a representative compound from a series of benzoic acid derivatives, wherein the following are also included:



Compound	R1	R2	Formula
262655	CH2CH2OCH2CH=C(Me)-CH2CH2CH=C(Me)2	NH2	C ₂₀ H ₂₉ NO ₃
262656	(CH2)5OC6H13	NH2	C ₁₉ H ₃₁ NO ₃
262657	CH2OC10H21	NH2	C ₁₉ H ₃₁ NO ₃
262658	CH2OCH2CH2OC6H13	NH2	C ₁₇ H ₂₇ NO ₄
262659	(CH2)5OCH2CH(Et)Bu	NH2	C ₂₁ H ₃₅ NO ₃
262660	CH2CH2OCH2CH=C(Me)-CH2CH2CH=C(Me)2	OEt	C ₂₂ H ₃₂ O ₄
262661	CH2CH2OCH2CH=C(Me)-CH2CH2CH=C(Me)2	OH	C ₂₀ H ₂₈ O ₄

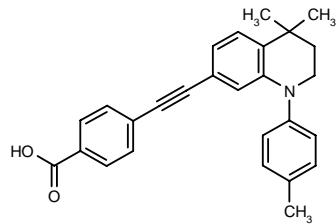
SOURCE – Kao.

REFERENCES

1. Ohashi, Y. et al. (Kao Corp.) *Benzoic acid derivs. and medicines containing the same*. JP 97323955.

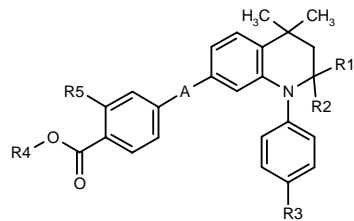
262354

4-[4,4-Dimethyl-1-(4-methylphenyl)-1,2,3,4-tetrahydroquinolin-7-ylethynyl]benzoic acid



C27-H25-N-O2; Mol wt: 395.50

ACTION – Compound with retinoid-like activity, tested *in vitro* for its binding affinity for the receptor subtypes RAR α (K_i = 13 nM), RAR β (K_i = 3 nM) and RAR γ (K_i = 9 nM). It acts as a retinoid inverse agonist, as demonstrated by its ability to inhibit basal luciferase activity in a transactivation assay in CV-1 cells. Preferably for the topical treatment of dermatoses such as severe cystic acne or psoriasis. Within this series of *N*-aryl substituted tetrahydroquinolines, the following are also included:



Compound	R1	R2	R3	R4	R5	A	Formula
262435	H	H	Me	Et	H	ethynylene	C ₂₉ H ₂₉ NO ₂
262436	H	H	H	H	H	ethynylene	C ₂₆ H ₂₃ NO ₂
262437	H	H	Me	H	F	ethynylene	C ₂₇ H ₂₄ FNO ₂
262438	H	H	Me	H	H	CH=CH	C ₂₇ H ₂₇ NO ₂
262439	-O-		Me	H	H	ethynylene	C ₂₇ H ₂₃ NO ₃
262440	H	H	Me	H	H	NHCO	C ₂₆ H ₂₆ N ₂ O ₃

SOURCE – Allergan.

REFERENCES

1. Beard, R.L. et al. (Allergan, Inc.) *N*-Aryl substd. tetrahydroquinolines having retinoid agonist, retinoid antagonist or retinoid inverse agonist type biological activity. US 5739338.

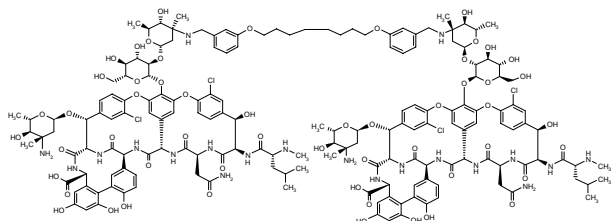
ANTIINFECTIVE THERAPY

MISCELLANEOUS ANTIBIOTICS

257238

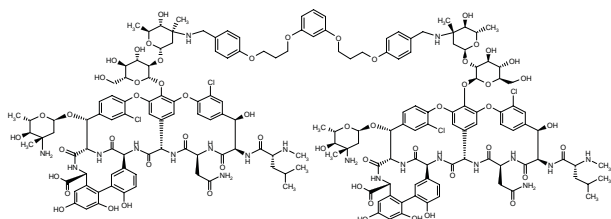
N^{3''},*N*^{3'''}-(Octane-1,8-diyl)bis(oxy)bis(3,1-phenylenemethylene)bis[(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-22-(3-amino-2,3,6-trideoxy-3-*C*-methyl-β-*L*-galactopyranosyloxy)-44-[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-β-*L*-galactopyranosyl)-β-*D*-glucopyranosyloxy]-3-(carbamoylmethyl)-10,19-dichloro-7,28,30,32-tetrahydroxy-6-(*N*-methyl-*D*-leucylamino)-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38*a*-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,36-(imino-methano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid]

N^{3''},*N*^{3'''}-(Octane-1,8-diyl)bis(oxy)bis(3,1-phenylenemethylene)bis[22-(3-amino-2,3,6-trideoxy-3-*C*-methyl-β-*L*-galactopyranosyloxy)vancomycin]

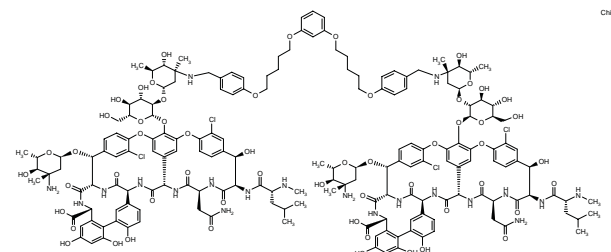


C168-H202-CI4-N20-O54; Mol wt: 3507.36

ACTION – Glycopeptide antibiotic active against Gram-positive bacteria, particularly vancomycin-resistant enterococci, e.g., representative strains of *Enterococcus faecium* and *Enterococcus faecalis* (mean geometric MIC = 1.7 µg/ml against resistant strains; mean geometric MIC = 0.5 µg/ml against sensitive strains). Other representative compounds within this series of glycopeptide dimers include the following:



258755: C172-H202-CI4-N20-O56



258756: C176-H210-CI4-N20-O56

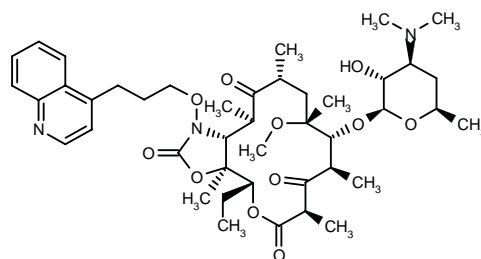
SOURCE – Lilly.

REFERENCES

1. Stack, D.R. and Thompson, R.C. (Eli Lilly & Co.) *Glycopeptide cpds.* WO 9738706.

261552

(3*aS*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15*aR*)-4-Ethyl-11-methoxy-3*a*,7,9,11,13,15-hexamethyl-1-[3-(4-quinolyl)propoxy]-10-[3,4,6-trideoxy-4-(dimethylamino)-β-*D*-glucopyranosyloxy]perhydrooxacyclotetradecino[4,3-*d*]-oxazole-2,6,8,14-tetraone



C43-H63-N3-O11; Mol wt: 797.98

ACTION – Antibacterial agent, an erythromycin derivative with particularly potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.04 µg/ml), *Streptococcus pyogenes* 02A1UC1 (MIC = 0.02 µg/ml or less), *Streptococcus agalactiae* 02B1HT1 (MIC = 0.02 µg/ml or less), *Streptococcus faecalis* 02D2UC1 (MIC = 0.02 µg/ml or less) and *Streptococcus pneumoniae* 032UC1 (MIC = 0.02 µg/ml or less). Also reported to be active against *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, *Ureaplasma*, *Toxoplasma* and *Mycobacteria*.

SOURCE – Hoechst Marion Roussel.

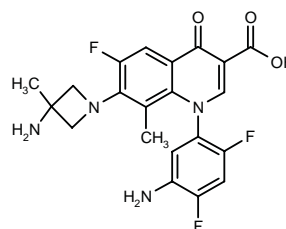
REFERENCES

1. Agouridas, C. et al. (Roussel Uclaf) *Novel erythromycin derivs., method for preparing same and use thereof as drugs.* WO 9803530.

MISCELLANEOUS
ANTIBACTERIAL DRUGS

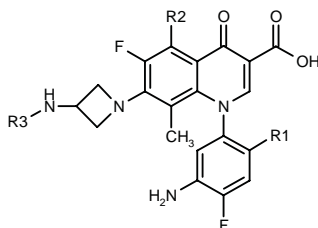
257726

7-(3-Amino-3-methylazetidin-1-yl)-1-(5-amino-2,4-difluorophenyl)-6-fluoro-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C21-H19-F3-N4-O3; Mol wt: 432.40

ACTION – Quinolone antibacterial agent with good oral absorption and metabolic stability, active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P and *Pseudomonas aeruginosa* IFO 3445 (MIC = 0.006 and 0.1 µg/ml, respectively); no phototoxicity was observed in mice administered a dose of 40 mg/kg i.v. Within this series of pyridonecarboxylic acid derivatives, the following are also included:



Compound	R1	R2	R3	Formula
261339	F	H	H	C ₂₀ H ₁₇ F ₃ N ₄ O ₃
261340	F	H	Me	C ₂₁ H ₁₉ F ₃ N ₄ O ₃
261341	Me	H	H	C ₂₁ H ₂₀ F ₂ N ₄ O ₃
261342	F	Me	H	C ₂₁ H ₁₉ F ₃ N ₄ O ₃

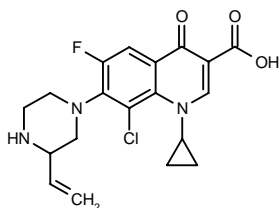
SOURCE – Wakunaga.

REFERENCES

1. Yazaki, A. et al. (Wakunaga Pharm. Co., Ltd.) *Novel pyridonecarboxylic acid derivs. or salts thereof and antibacterial agents containing the same as the active ingredient.* WO 9740036.

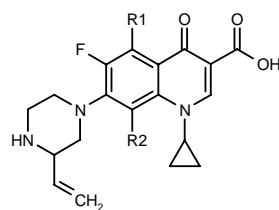
261163

8-Chloro-1-cyclopropyl-6-fluoro-4-oxo-7-(3-vinyl-1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid



C19-H19-Cl-F-N3-O3; Mol wt: 391.83

ACTION – Quinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria including antibiotic-resistant strains, and low toxicity. *In vitro*, it was active against a broad range of microorganisms including *Escherichia coli* Ec 9675 (MIC = 1 µg/ml), *Staphylococcus* sp. 2706 (MIC = 0.06 µg/ml), *Salmonella* sp. S 9656 (MIC = 0.5 µg/ml), *Bordetella bronchiseptica* B 9601 (MIC = 0.25 µg/ml), *Pseudomonas* sp. P 9510 (MIC = 0.5 µg/ml), *Streptococcus agalactiae* Scc 9513 (MIC = 0.5 µg/ml) and *Mycoplasma* spp. (MIC = 0.03-0.06 µg/ml). *In vivo*, it inhibited *E. coli* 6200-induced mortality in chickens following p.o. administration (ED₉₀ = 1.25 mg/kg). Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
261795	NH2	F	C ₁₉ H ₂₀ F ₂ N ₄ O ₃
261796	H	OCHF2	C ₂₀ H ₂₀ F ₃ N ₄ O ₄

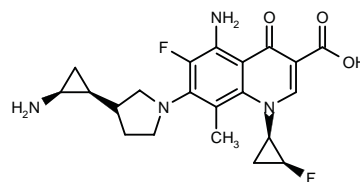
SOURCE – Bayer.

REFERENCES

1. Himmler, T. et al. (Bayer AG) *Quinolone carboxylic acids substd. by 7-(3-vinyl-1,4-piperazine-1-yl).* WO 9800421.

261219

5-Amino-7-[3-[2(*S*)-amino-1(*S*)-cyclopropyl]pyrrolidin-1-yl]-6-fluoro-1-[2(*S*)-fluoro-1(*R*)-cyclopropyl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C21-H24-F2-N4-O3; Mol wt: 418.44

ACTION – Quinolone antibacterial agent with potent, broad-spectrum activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 870307 (MIC = 0.025 µg/ml), *S. aureus* 209P (MIC = 0.003 µg/ml or less), *Staphylococcus epidermidis* 56500 (MIC = 0.006 µg/ml), *Streptococcus pyogenes* G-36 (MIC = 0.006 µg/ml), *Streptococcus faecalis* ATCC-19433 (MIC = 0.025 µg/ml), *Pseudomonas aeruginosa* 32121 (MIC = 0.10 µg/ml) and *Escherichia coli* NIHJ (MIC = 0.003 µg/ml or less).

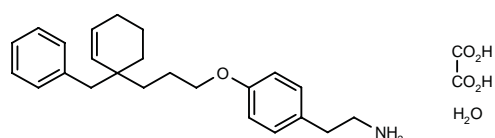
SOURCE – Daiichi Pharm.

REFERENCES

1. Takemura, M. et al. (Daiichi Pharm. Co., Ltd.) *cis-Subst. aminocyclopropane derivs.* JP 98081682, WO 9802431.

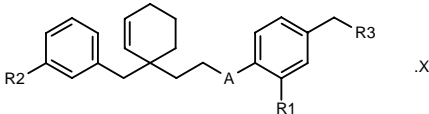
260119

2-[4-[3-(1-Benzyl-2-cyclohexen-1-yl)propoxy]phenyl]-ethylamine oxalate hydrate

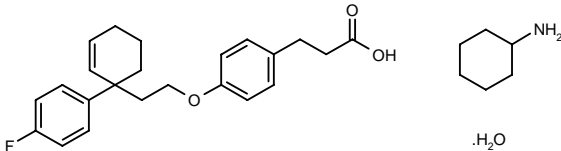


C24-H31-N-O.C2-H2-O4.H2-O; Mol wt: 457.57

ACTION – Antibacterial and antifungal agent that inhibits histidine protein kinase, as demonstrated by inhibition of the autophosphorylation of kinase A and the transphosphorylation of SPoOF. It completely inhibited the growth of several bacterial and fungal species at a concentration of 4-8 µg/ml including strains of *Escherichia coli*, *Candida tropicalis*, *Aspergillus niger*, *Enterococcus faecalis*, *Enterococcus faecium* and methicillin-sensitive and -resistant *Staphylococcus aureus*. Other specifically claimed 2-disubstituted cyclohexenyl and cyclohexyl compounds include the following:



Compound	R1	R2	R3	A	X	Formula
262398	H	Cl	NH2	O	oxalate	C ₂₂ H ₂₆ ClNO .C ₂ H ₂ O ₄
262399	H	Cl	NHC(=NH)NH2	O	HNO3	C ₂₃ H ₂₈ ClN ₃ O .HNO ₃
262400	H	H	3-pyrrolidinyl-CH2-CH2NHCH2CH2	O	oxalate hydrate	C ₃₀ H ₄₂ N ₂ O .C ₂ H ₂ O ₄ .H ₂ O
262401	OMe	H	NH2	O	oxalate hydrate	C ₂₃ H ₂₉ NO ₂ .C ₂ H ₂ O ₄ .H ₂ O
262402	OMe	H	CH2NHEt	NH	oxalate hydrate	C ₂₆ H ₃₆ N ₂ O .C ₂ H ₂ O ₄ .H ₂ O
262404	H	H	(CH2)3NH2	O	oxalate hydrate	C ₂₅ H ₃₃ NO .C ₂ H ₂ O ₄ .H ₂ O
262405	H	Cl	CH2NHC(=NH)NH2	O	oxalate hydrate	C ₂₄ H ₃₀ ClN ₃ O .C ₂ H ₂ O ₄ .H ₂ O



262403: C23-H25-F-O3.C6-H13-N.H2-O

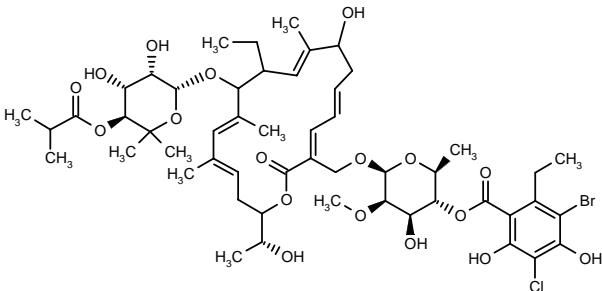
SOURCE – Ortho.

REFERENCES

1. Chen, R.H. et al. (Ortho Pharm. Corp.) 2-Disubstd. cyclohexenyl and cyclohexyl antimicrobial agents. WO 9748675.

261229

2-[4-O-(3-Bromo-5-chloro-2-ethyl-4,6-dihydroxybenzoyl)-6-deoxy-β-L-mannopyranosyloxymethyl]-10-ethyl-7,18(*R*)-dihydroxy-11-(6-deoxy-4-*O*-isobutyryl-5-*C*-methyl-β-D-mannopyranosyloxy)-8,12,14-trimethyl-2(*E*),4(*E*),8(*E*),12(*E*),14(*E*)-nonadecatetraeno-17-lactone



C52-H74-Br-Cl-O18; Mol wt: 1102.50

ACTION – Antibacterial agent, a brominated tiacumicin analog with activity against a variety of bacterial pathogens, particularly *Clostridium difficile*. When tested *in vitro*, it was active against *Clostridium perfringens* ATCC 13124 (MIC = 0.03 mg/ml) and several strains of *C. difficile* (MIC = 0.06 mg/ml). The compound may be obtained by modifying the process for producing tiacumicin antibiotics, which are isolated from the fermentation broth and mycelium of *Dactylosporangium auranticum* subsp. *hamdenensis* subsp. nov.

SOURCE – Abbott.

REFERENCES

1. Hochlowski, J.E. et al. (Abbott Labs.) Bromotiacumicin cpds. WO 9802447.

261527

Cyclo(cysteinyI-tyrosyl-cysteinyI-arginyl-arginyl-arginyl-phenylalanyl-cysteinyI-valyl-cysteinyI-valyl-glycyl-arginyl-tryptophanyl-leucyl)

C83-H128-N28-O16-S4; Mol wt: 1902.34

ACTION – Antimicrobial cyclic peptide with a broad spectrum of activity and improved efficacy, bioavailability and serum half-life as compared to noncyclized analogs. MICs against *Pseudomonas aeruginosa* ATCC 9027 and methicillin-resistant *Staphylococcus aureus* ATCC 33591 were 8 and 2 µg/ml, respectively. Within this series of cyclic peptides, the following are also included:

Cyclo(cysteinyI-tyrosyl-cysteinyI-arginyl-arginyl-arginyl-phenylalanyl-cysteinyI-valyl-cysteinyI-valyl-tryptophanyl-tyrosyl)

262177: C78-H111-N23-O15-S4

Cyclo(cysteinyI-tyrosyl-cysteinyI-arginyl-arginyl-arginyl-phenylalanyl-cysteinyI-valyl-cysteinyI-valyl-arginyl-leucyl)

262178: C70-H115-N25-O14-S4

Cyclo(cysteinyI-tyrosyl-cysteinyI-arginyl-arginyl-arginyl-phenylalanyl-cysteinyI-valyl-cysteinyI-valyl-glycyl-arginyl-arginyl-glycyl-glycyl-arginyl-leucyl)

262179: C88-H148-N36-O19-S4

Cyclo(cysteinyI-tyrosyl-cysteinyI-arginyl-arginyl-arginyl-phenylalanyl-cysteinyI-valyl-cysteinyI-valyl-tryptophanyl-leucyl)

262180: C75-H113-N23-O14-S4

SOURCE – IntraBiotics.

REFERENCES

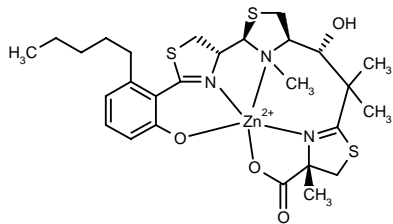
1. Chang, C. et al. (IntraBiotics Pharm., Inc.) Cyclic peptides having broad spectrum antimicrobial activity. WO 9803192.

ANTIMYCOBACTERIAL AGENTS

MICACOCIDIN A

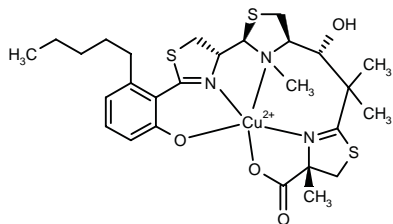
262036

[2-[2(*S*)-Hydroxy-1,1-dimethyl-2-[2(*R*)-[2-(2-hydroxy-6-pentylphenyl)-4,5-dihydrothiazol-4(*R*)-yl]-3-methylthiazolidin-4(*R*)-yl]ethyl]-4-methyl-4,5-dihydrothiazole-4(*S*)-carboxylato(2-)]zinc

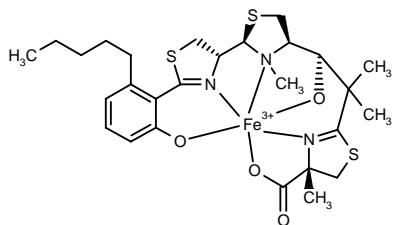


C27-H37-N3-O4-S3-Zn; Mol wt: 629.09

ACTION – Antibacterial agent isolated from a culture of *Pseudomonas* sp. 57-250 (FERM P-14235), with excellent activity against *Mycoplasma* spp. such as *Mycoplasma pneumoniae* Mac (MIC = 0.0065 µg/ml or less), *Mycoplasma hyopneumoniae* ST-11 (MIC = 0.025 µg/ml), *Mycoplasma gallisepticum* S6 (MIC = 0.1 µg/ml) and *Mycoplasma synoviae* 1853 (MIC = 0.78 µg/nml), and poor activity against other bacteria tested including *Staphylococcus aureus* FDA 209P JC-1 (MIC = 25 µg/ml), *Bordetella bronchiseptica* H-16 (MIC = 25 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC > 25 µg/ml) and *Streptococcus* sp. SN 86119 (MIC = 6.25 µg/ml). Other antibiotics isolated from the same source include the following:



Micacocidin B [262037]: C27-H37-Cu-N3-O4-S3



Micacocidin C [262038]: C27-H36-Fe-N3-O4-S3

SOURCE – Shionogi.

REFERENCES

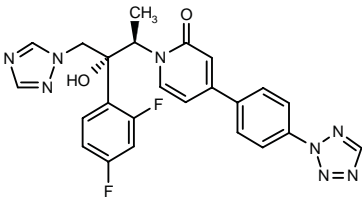
1. Hayase, Y. et al. (Shionogi & Co., Ltd.) *Micacocidin derivs.* WO 9729096.
2. Takeda, R. et al. (Shionogi & Co., Ltd.) *Novel antibiotic and process for producing the same.* EP 727420, US 5707838, WO 9604262.
3. Ino, A. et al. *Chemical structure and total synthesis of new antimycoplasma antibiotic micacocidin.* Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 1996, 38: 121.

4. Kobayashi, S. et al. *Micacocidin A, B and C, novel antimycoplasma agents from Pseudomonas sp. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activities.* J Antibiot 1998, 51(3): 323.
5. Kobayashi, S. et al. *Micacocidin A, B and C, novel antimycoplasma agents from Pseudomonas sp. II. Structure elucidation.* J Antibiot 1998, 51(3): 328.

ANTIFUNGAL AGENTS

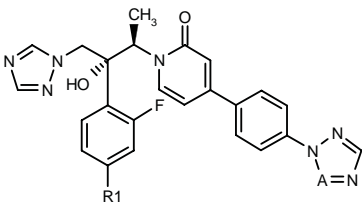
261876

(*R,R*)-1-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1,2,4-triazol-1-yl)propyl]-4-[4-(2-tetrazolyl)phenyl]pyridin-2(1*H*)-one



C24-H20-F2-N8-O2; Mol wt: 490.47

ACTION – Orally active azole antifungal agent, as demonstrated in a murine model of systemic candidosis (ED₅₀ = 0.041 mg/kg p.o.). Within this series of triazole derivatives, the following are also included:



Compound	R1	A	Formula
262693	F	CH	C ₂₅ H ₂₁ F ₂ N ₇ O ₂
262694	H	CH	C ₂₅ H ₂₂ FN ₇ O ₂
262695	H	N	C ₂₄ H ₂₁ FN ₈ O ₂

SOURCE – Takeda.

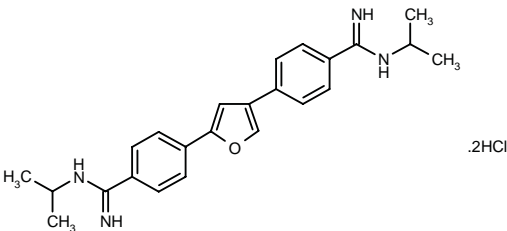
REFERENCES

1. Ito, K. et al. (Takeda Chem. Ind., Ltd.) *Azole cpds., preparation method thereof and their use.* JP 98045750.

DB-480

261722

4,4'-(Furan-2,4-diyl)bis(*N*¹-isopropylbenzamidine) dihydrochloride



C24-H28-N4-O.2HCl; Mol wt: 461.43

ACTION – Antimicrobial agent with activity against *Pneumocystis carinii* pneumonia in immunosuppressed rats and reduced DNA binding affinity.

SOURCES – Georgia State Univ., Atlanta, GA (US); Univ. North Carolina, Chapel Hill, NC (US).

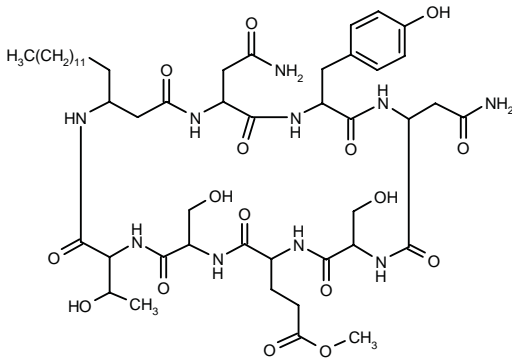
REFERENCES

1. Francesconi, I. et al. *2,4-Bis-[(4-amidino)phenyl]furans as anti-Pneumocystis carinii agents*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 013.

YL-03831B-A

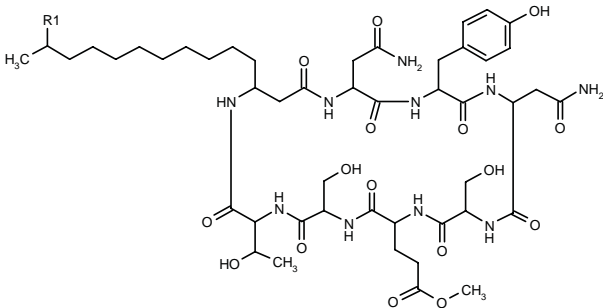
258454

DL-Asparaginy-DL-tyrosyl-DL-asparaginy-DL-seryl-DL-glutaminy-DL-seryl-DL-threony-DL-(3-aminohexadecanoic acid) C-1.8-N-2.1-lactam



C49-H78-N10-O16; Mol wt: 1063.21

ACTION – Antifungal agent isolated from *Bacillus* sp. STC4546 (FERM P-15614), reported to be effective against *Candida albicans* YFC-48, *Cryptococcus* sp. YFC-75, *Aspergillus niger* YFC-36 and *Trichophyton interdigitale* YFC-174, among others. Other related compounds include the following:



Compound	R1	Formula
YL-03831B-B [262703]	Me	C ₄₈ H ₇₆ N ₁₀ O ₁₆
YL-03831B-C [262704]	H	C ₄₇ H ₇₄ N ₁₀ O ₁₆

SOURCES – Sagami; Yamanouchi.

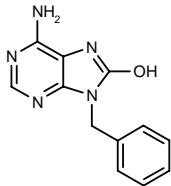
REFERENCES

1. Takahashi, I. et al. (Yamanouchi Pharm. Co., Ltd.; Sagami Chem. Res. Center) *Novel cyclic peptides*. JP 97301997.

ANTIVIRAL DRUGS

261209

9-Benzyl-8-hydroxyadenine



C12-H11-N5-O; Mol wt: 241.25

ACTION – Antiviral and antineoplastic agent that acts by inducing the production of cytokines such as interferon, tumor necrosis factor-α (TNF-α) and IL-6.

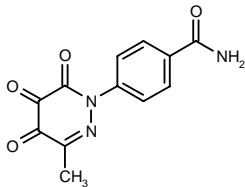
SOURCE – Japan Energy.

REFERENCES

1. Hirota, K. et al. (Japan Energy Corp.) *Novel purine derivs*. WO 9801448.

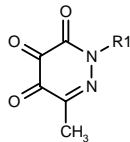
261535

4-(3-Methyl-4,5,6-trioxo-1,4,5,6-tetrahydropyridazin-1-yl)benzamide



C12-H9-N3-O4; Mol wt: 259.22

ACTION – Antiviral agent for the treatment or prevention of influenza virus infection that appears to inhibit influenza virus transcription by inhibiting cleavage of cap 1 RNA by the virus. Other specifically claimed susbtituted pyridazine derivatives include the following:



Compound	R1	Formula
262356	4-Me-3-(NH2SO2)-Ph	C ₁₂ H ₁₁ N ₃ O ₅ S
262357	2-Cl-5-(MeNHSO2)-Ph	C ₁₂ H ₁₀ ClN ₃ O ₅ S
262358	4-(MeNHSO2)-Ph	C ₁₂ H ₁₁ N ₃ O ₅ S
262359	4-(PhNHSO2)-Ph	C ₁₇ H ₁₃ N ₃ O ₅ S
262360	4-(AcNHSO2)-Ph	C ₁₃ H ₁₁ N ₃ O ₆ S
262361	4-(3-Pyr-NHSO2)-Ph	C ₁₆ H ₁₂ N ₄ O ₅ S
262362	1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-6-yl	C ₁₂ H ₇ N ₃ O ₆ S

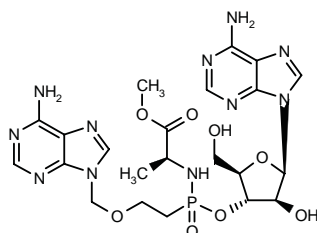
SOURCE – ViroPharma.

REFERENCES

1. Diana, G.C. et al. (ViroPharma, Inc.) *Cpds., compsns. and methods for treating influenza*. WO 9803487.

261899

2-(Adenin-9-ylmethoxy)-*N*-[1(*S*)-methoxycarbonyl]ethylphosphonamidic acid 9-(β-D-arabino-furanosyl)adenin-3'-*O*-yl ester



C22-H30-N11-O8-P; Mol wt: 607.52

ACTION – Antiviral agent, an adenylate analog with activity against herpes simplex virus type 1 (HSV-1), HSV-2 and varicella-zoster virus in HeLa cell cultures (IC₅₀ = 0.38, 0.88 and 4.82 μg/ml, respectively), and increased lipophilicity and resistance to adenosine deaminase compared to related compounds.

SOURCE – Natl. Science Council, Taipei (TW).

REFERENCES

1. Hwu, J.R. et al. (Natl. Sci. Council [TW]) *Adenylate analogs as potent anti-herpes virus agents*. US 5733890.

FR-202306

259198

C10-H12-O5; Mol wt: 212.20

ACTION – Antiviral agent derived from the known compound FR-198248⁺, proven to induce 100% inhibition of influenza virus A/PR/8/34 replication at a concentration of 10 μg/ml in a plaque formation assay in MDCK cells.

SOURCE – Fujisawa.

REFERENCES

1. Nishihara, Y. et al. (Fujisawa Pharm. Co., Ltd.) *FR198248 and FR202306 substances*. JP 97316090.

*Drug Data Rep 1998, 20(2): 154.

RO-25-3036

261662

Polyethylene glycol (PEG) covalently linked to interferon alfa-2a

ACTION – Antiviral agent, a pegylated (polyethylene glycol-modified) human interferon alfa-2a with a longer half-life in blood and within tumors than unmodified

interferon alfa-2a, useful for the treatment of chronic hepatitis C (HCV). In a phase I study in healthy volunteers, the required dosing frequency decreased from three times weekly to twice weekly, which was confirmed in a phase II study in HCV patients.

SOURCE – Roche.

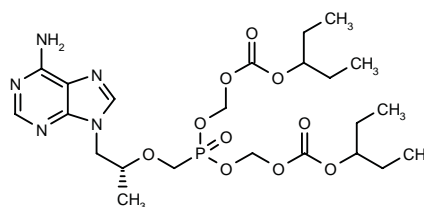
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1. Palleroni, A.V. et al. *The in vivo fate of PEG-interferon α-2a (Ro 25-3036) in tumor bearing mice*. Proc Amer Assoc Cancer Res 1994, 35: Abst 1845.
2. Xu, Z.-X. et al. *PK/PD modeling approach to support clinical development of a long-acting interferon (Ro 25-3036) for the treatment of chronic hepatitis C*. Clin Pharmacol Ther 1998, 63(2): Abst P1-101.

AIDS MEDICINES

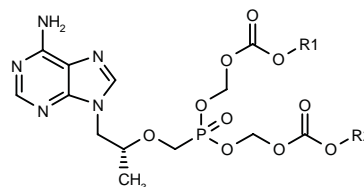
261589

[2-(Adenin-9-yl)-1(*R*)-methylethoxymethyl]phosphonic acid bis(2-ethylpropoxycarbonyloxymethyl) ester



C23-H38-N5-O10-P; Mol wt: 575.55

ACTION – Carbonate prodrug of the antiviral agent PMPA found to exhibit increased potency against HIV-1 compared to PMPA (IC₅₀ < 0.001 μM vs. 0.5 μM for PMPA) and an improved selectivity index (SI) in spite of increased cytotoxicity (CC₅₀ = 40 μM vs. 250 μM for PMPA; SI = 40,000 vs. 500 for PMPA). The increased activity is believed to be due to increased cellular uptake of the prodrug, possibly due to its increased lipophilicity. Other related nucleotide analogs include the following:



Compound	R1=R2	Formula
262953	Et	C ₁₇ H ₂₆ N ₅ O ₁₀ P
262954	i-Bu	C ₂₁ H ₃₄ N ₅ O ₁₀ P
262955	t-Bu	C ₂₁ H ₃₄ N ₅ O ₁₀ P
262956	t-BuCH ₂	C ₂₃ H ₃₈ N ₅ O ₁₀ P

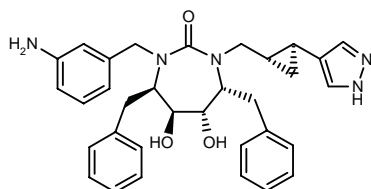
SOURCE – Gilead Sciences.

REFERENCES

1. Arimilli, M.N. et al. (Gilead Sciences, Inc.) *Nucleotide analogs*. WO 9804569.

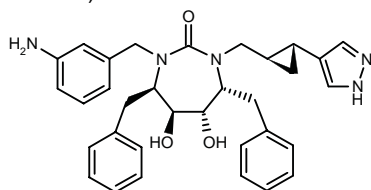
261720

[4*R*-(4 α ,5 α ,6 β ,7 β)]-3-(3-Aminobenzyl)-4,7-dibenzyl-5,6-dihydroxy-1-[2(*S*)-(1*H*-pyrazol-4-yl)cycloprop-1(*S*)-ylmethyl]perhydro-1,3-diazepin-2-one



C33-H37-N5-O3; Mol wt: 551.69

ACTION – Antiviral agent for AIDS, a potent HIV protease inhibitor ($K_i = 0.20$ nM) discovered as part of an effort to increase the oral bioavailability of cyclic ureas. The (*R,R*)-cyclopropane diastereoisomer (**261721**) is 10 times less active ($K_i = 2.7$ nM).



261721: C33-H37-N5-O3

SOURCE – DuPont Merck.

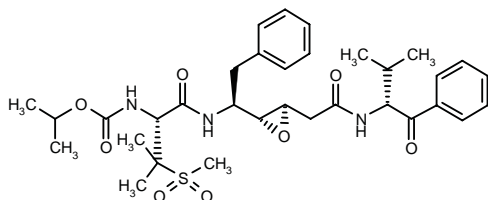
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1. Han, W. et al. *Flexible docking, synthesis and biological evaluation of N-[(4-pyrazolyl)cyclopropylmethyl] cyclic ureas as HIV protease inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MED1 026.

LB-71350***252182**

N-[1(*R*)-[*N*-[4-[*N*-[1(*R*)-Benzoyl-2-methylpropyl]-carbamoyl]-1(*S*)-benzyl-2(*R*),3(*S*)-epoxybutyl]carbamoyl]-2-methyl-2-(methylsulfonyl)propyl]carbamic acid isopropyl ester

N-[1(*R*)-Benzoyl-2-methylpropyl]-3(*S*),4(*R*)-epoxy-5(*S*)-[*N*-(isopropoxycarbonyl)-3-(methanesulfonyl)-*L*-valylamino]-6-phenylhexanamide



C33-H45-N3-O8-S; Mol wt: 643.79

ACTION – Antiviral agent for AIDS, an irreversible inhibitor of HIV-1 protease with an EC_{50} of 6.5 nM and EC_{95} of 31.3 nM in HIV-1-infected MT-2 cells. In dogs and rats, the oral bioavailability was 68 and 44%, respectively, and the half-life was about 20 min, and the bioavailability and half-life in humans are expected to be greater than in these animal species.

SOURCE – LG Chem.

REFERENCES

1. Kim, S.-C. et al. (LG Chem., Ltd.) *Cis-epoxide derivate useful as irreversible HIV protease inhibitor and process for its preparation*. EP 770606, JP 97124627.
2. Jeong, Y.-N. et al. *High-performance liquid chromatographic assay of a new HIV-1 protease inhibitor, LB71350, in the plasma of dogs*. J Chromatog B 1997, 703(1-2): 284.
3. Jeong, Y.-N. et al. *Pharmacokinetics of the irreversible HIV-1 protease inhibitor, LB71350, in rats and dogs*. Pharm Res 1996, 13(9, Suppl.): Abst PPDM 8375.

*Identified compound **252182** Drug Data Rep 1997, 19(9): 826.

MCPP**261232**

Human monocyte chemotactic proprotein

ACTION – Human monocyte chemotactic proprotein produced by genetic engineering, potentially useful in the treatment of autoimmune diseases such as AIDS, asthma, rheumatoid arthritis, non-insulin-dependent diabetes mellitus and cancer of the breast or bladder.

SOURCE – Incyte.

REFERENCES

1. Coleman, R. et al. (Incyte Pharm., Inc.) *Human monocyte chemotactic proprotein*. WO 9802459.

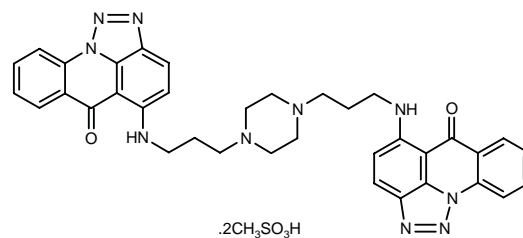
TEMACRAZINE MESILATE**246655**

5,5'-[(Piperazine-1,4-diyl)bis(propane-1,3-diylidimino)]-bis(6*H*-[1,2,3]triazolo[4,5,1-*de*]acridin-6-one) dimethanesulfonate

NSC-687025

NSC-682405 (as free base)

WMC-70 (as free base)



C36-H34-N10-O2.2C-H4-O3-S; Mol wt: 830.93

M.p. 240-6 °C (decomp.); **free base**, **m.p.** 242-5 °C.

ACTION – Antiviral agent for AIDS that selectively inhibits HIV-1 transcription during the postintegrative phase of virus replication. It inhibited the replication of laboratory strains and clinical isolates of HIV-1, including drug-resistant isolates, with EC_{50} values of 1.1-72.0 nM versus IC_{50} values for cytotoxicity in various cell lines of about 1-10 μ M. *In vivo* anti-HIV-1 activity was demonstrated at nontoxic concentrations in a murine hollow fiber model.

SOURCES – Natl. Cancer Inst.-Frederick Cancer Res. Dev. Center, Frederick, MD (US); Southern Res. Inst.-Frederick Res. Center, Frederick, MD (US).

REFERENCES

1. Michejda, C.J. et al. (Dept. Health Human Services [USA]) *Acridone-derived cpds. useful as antineoplastic and antiretroviral agents*. WO 9738999.
2. Cholody, W.M. et al. *Some linker-modified antineoplastic bisimidazoacridones are potent inhibitors of HIV-1, with unique mechanism of action*. Proc Amer Assoc Cancer Res 1998, 39: Abst 2069.
3. Turpin, J.A. et al. *Identification of a novel bisimidazoacridone that inhibits HIV-1 replication by prevention of formation of post-integrative full-length RNA transcripts*. 4th Conf Retroviruses Opportunistic Infect (Jan 22-26, Washington DC) 1997, Abst.
4. Turpin, J.A. et al. *Inhibition of acute, latent-, and chronic-phase human immunodeficiency virus type 1 (HIV-1) replication by a bistriazoloacridone analog that selectively inhibits HIV-1 transcription*. Antimicrob Agents Chemother 1998, 42(3): 487.

TREATMENT OF PROTOZOAL DISEASES

rTLTF

261594

Recombinant trypanosome-derived lymphocyte triggering factor

ACTION – Recombinant form of a glycoprotein secreted by *Trypanosoma brucei* that has been shown to stimulate CD8+ T-cells to release interferon gamma, which is known to stimulate parasite growth. This peptide may be used to prepare vaccines against African sleeping sickness (African trypanosomiasis). Additionally, monoclonal antibodies directed against this peptide are also claimed for the treatment of African sleeping sickness.

SOURCES – Univ. Iowa Res. Found.; SBL Vaccin.

REFERENCES

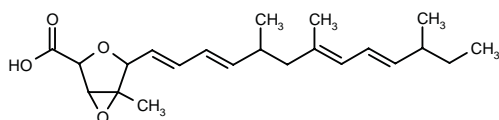
1. Vaidya, T. et al. (SBL Vaccin AB; Univ. Iowa Res. Found., Inc.) *Lymphocyte stimulating factor from Trypanosoma*. WO 9804588.

TREATMENT OF HELMINTHIC DISEASES

FT-0554

262486

3,4-Epoxy-4-methyl-5-[5,7,11-trimethyl-1(*E*),3(*E*),7(*E*),9(*E*)-tridecatetraenyl]tetrahydrofuran-2-carboxylic acid



C22-H32-O4; Mol wt: 360.49

ACTION – Anthelmintic agent produced by *Aspergillus niger* FT-0554, an NADH-fumarate reductase (NFRD) inhibitor giving an IC₅₀ of 2.8 μM against NFRD activity from pig roundworm smooth muscle mitochondrial fractions.

SOURCE – Kitasato Inst., Tokyo (JP).

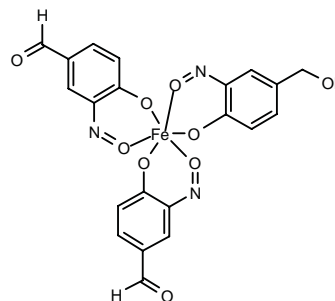
REFERENCES

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K-96-0188

262487

Bis[4-formyl-2-(nitroso-κO)phenolato-κO][4-(hydroxymethyl)-2-(nitroso-κO)phenolato-κO]iron



C21-H14-Fe-N3-O9; Mol wt: 508.20

ACTION – Antiparasitic agent with antibacterial activity against some microorganisms such as *Acholeplasma laidlawii*, isolated from *Streptomyces* sp. K96-0188.

SOURCE – Kitasato Inst., Tokyo (JP).

REFERENCES

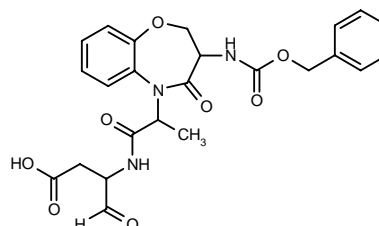
1. Enomoto, T. et al. *Isolation and structure of novel antibiotics K96-0188 produced by ray fungi*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)12-19.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

258433

3-[2-[3-(Benzyloxycarbonylamino)-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]propionamido]-4-oxobutyric acid



C24-H25-N3-O8; Mol wt: 483.48

ACTION – Agent for the treatment of rheumatoid arthritis, an inhibitor of cysteine proteases such as interleukin-1β-converting enzyme (ICE; IC₅₀ = 10 nM).

REFERENCES

1. Michejda, C.J. et al. (Dept. Health Human Services [USA]) *Acridone-derived cpds. useful as antineoplastic and antiretroviral agents*. WO 9738999.
2. Cholody, W.M. et al. *Some linker-modified antineoplastic bisimidazoacridones are potent inhibitors of HIV-1, with unique mechanism of action*. Proc Amer Assoc Cancer Res 1998, 39: Abst 2069.
3. Turpin, J.A. et al. *Identification of a novel bisimidazoacridone that inhibits HIV-1 replication by prevention of formation of post-integrative full-length RNA transcripts*. 4th Conf Retroviruses Opportunistic Infect (Jan 22-26, Washington DC) 1997, Abst.
4. Turpin, J.A. et al. *Inhibition of acute, latent-, and chronic-phase human immunodeficiency virus type 1 (HIV-1) replication by a bistriazoloacridone analog that selectively inhibits HIV-1 transcription*. Antimicrob Agents Chemother 1998, 42(3): 487.

TREATMENT OF PROTOZOAL DISEASES

rTLTF

261594

Recombinant trypanosome-derived lymphocyte triggering factor

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SOURCES – Univ. Iowa Res. Found.; SBL Vaccin.

REFERENCES

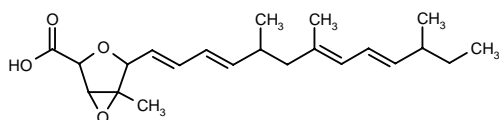
1. Vaidya, T. et al. (SBL Vaccin AB; Univ. Iowa Res. Found., Inc.) *Lymphocyte stimulating factor from Trypanosoma*. WO 9804588.

TREATMENT OF HELMINTHIC DISEASES

FT-0554

262486

3,4-Epoxy-4-methyl-5-[5,7,11-trimethyl-1(*E*),3(*E*),7(*E*),9(*E*)-tridecatetraenyl]tetrahydrofuran-2-carboxylic acid



C22-H32-O4; Mol wt: 360.49

ACTION – Anthelmintic agent produced by *Aspergillus niger* FT-0554, an NADH-fumarate reductase (NFRD) inhibitor giving an IC₅₀ of 2.8 μM against NFRD activity from pig roundworm smooth muscle mitochondrial fractions.

SOURCE – Kitasato Inst., Tokyo (JP).

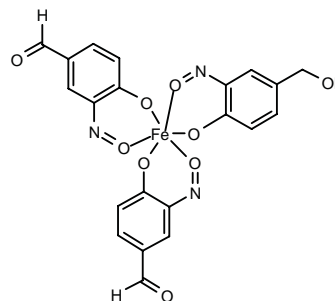
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K-96-0188

262487

Bis[4-formyl-2-(nitroso-κO)phenolato-κO][4-(hydroxymethyl)-2-(nitroso-κO)phenolato-κO]iron



C21-H14-Fe-N3-O9; Mol wt: 508.20

ACTION – Antiparasitic agent with antibacterial activity against some microorganisms such as *Acholeplasma laidlawii*, isolated from *Streptomyces* sp. K96-0188.

SOURCE – Kitasato Inst., Tokyo (JP).

REFERENCES

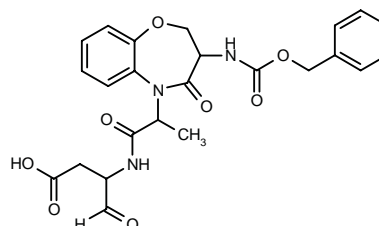
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

258433

3-[2-[3-(Benzyloxycarbonylamino)-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]propionamido]-4-oxobutyric acid



C24-H25-N3-O8; Mol wt: 483.48

ACTION – Agent for the treatment of rheumatoid arthritis, an inhibitor of cysteine proteases such as interleukin-1β-converting enzyme (ICE; IC₅₀ = 10 nM).

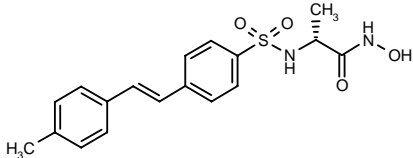
SOURCE – Takeda.

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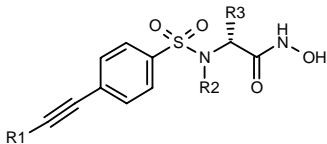
259894

*N*¹-Hydroxy-*N*²-[4-[2(*E*)-(4-methylphenyl)vinyl]phenylsulfonyl]-D-alaninamide



C18-H20-N2-O4-S; Mol wt: 360.43

ACTION – Agent for the treatment and prevention of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, arteriosclerosis, pulmonary emphysema, hepatic cirrhosis, corneal injury, cancer, autoimmune diseases and neovascularization, an inhibitor of matrix metalloproteinases such as gelatinase A (IC₅₀ = 0.2 nM against enzyme purified from human dermal fibroblasts). A representative compound from a series of phenylsulfonamide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
262567	4-Me-Ph	H	Me	C ₁₈ H ₁₈ N ₂ O ₄ S
262568	C ₅ H ₁₁	H	Me	C ₁₆ H ₂₂ N ₂ O ₄ S
262569	Pr	H	Me	C ₁₄ H ₁₈ N ₂ O ₄ S
262570	4-(1-imidazolyl)-Ph	Me	Me	C ₂₁ H ₂₀ N ₄ O ₄ S
262571	Pr	Me	Me	C ₁₅ H ₂₀ N ₂ O ₄ S
262572	H	H	CH ₂ CH ₂ CONH-CH ₂ CH ₂ Ph	C ₂₁ H ₂₃ N ₃ O ₅ S
262573	H	H	CH ₂ CH ₂ CONH-CH(Ph)CH ₂ Ph	C ₂₇ H ₂₇ N ₃ O ₅ S

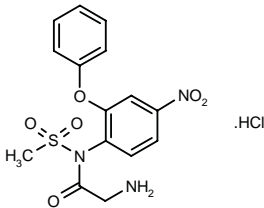
SOURCE – Ono.

REFERENCES

1. Takahashi, K. and Sugiura, T. (Ono Pharm. Co., Ltd.) *Phenylsulfonamide derivs.* WO 9745402.

260058

*N*¹-(Methanesulfonyl)-*N*¹-(2-phenoxy-4-nitrophenyl)-glycinamide hydrochloride



C15-H15-N3-O6-S.HCl; Mol wt: 401.82

ACTION – Antiinflammatory, analgesic and antipyretic agent shown to produce 27.8 and 52.3% inhibition of carrageenan-induced rat paw edema at doses of 1 and 5 mg/kg p.o., respectively. A representative compound within a series of 4-nitro-2-phenoxyulfonanilide derivatives, wherein the following are also included.

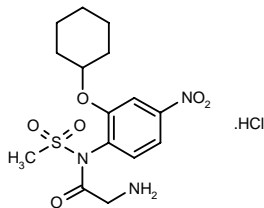
SOURCE – Taisho.

REFERENCES

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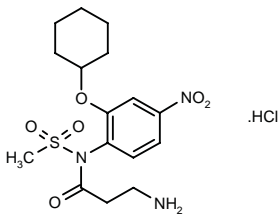
260099

*N*¹-(2-Cyclohexyloxy-4-nitrophenyl)-*N*¹-(methanesulfonyl)glycinamide hydrochloride



C15-H21-N3-O6-S.HCl; Mol wt: 407.87

ACTION – Antiinflammatory, analgesic and antipyretic agent proven to inhibit carrageenan-induced rat paw edema by 24.9% at a dose of 1 mg/kg p.o. Another representative compound within this series of 4-nitro-sulfonanilide derivatives is:



262531: C16-H23-N3-O6-S.HCl

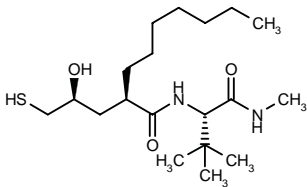
SOURCE – Taisho.

REFERENCES

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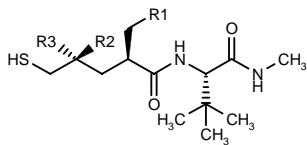
260862

N-[2,2-Dimethyl-1 (S)-(N-methylcarbamoyl)propyl]-2 (R)-[2 (S)-hydroxy-3-sulfanylpropyl]nonanamide



C35-H46-N2-O3-S; Mol wt: 574.82

ACTION – Inhibitor of matrix metalloproteinases such as collagenase (IC₅₀ = 30.0 nM) and stromelysin (96% inhibition at 0.1 μM), potentially useful in the treatment of rheumatoid arthritis and osteoarthritis. A representative compound from a series of mercaptoketones and mercaptoalcohols, wherein the following are also included:



Compound	R1	R2	R3	Formula
262019	i-Pr	H	OH	C ₁₆ H ₃₂ N ₂ O ₃ S
262020	i-Pr	OH	H	C ₁₆ H ₃₂ N ₂ O ₃ S
262021	C6H13		-O-	C ₁₉ H ₃₆ N ₂ O ₃ S
262022	i-Pr		-O-	C ₁₆ H ₃₀ N ₂ O ₃ S

SOURCE – American Cyanamid.

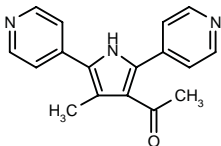
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1. Levin, J.I. (American Cyanamid Co.) *Mercaptoketones and mercaptoalcohols, a process for their preparation and their use as inhibitors of matrix metalloproteinases.* EP 818443, JP 98067737.

261218

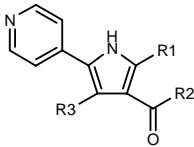
1-[4-Methyl-2,5-di(4-pyridyl)-1 H-pyrrol-3-yl]ethanone

3-Acetyl-4-methyl-2,5-di(4-pyridyl)-1 H-pyrrole



C17-H15-N3-O; Mol wt: 277.32

ACTION – Inhibitor of the production of cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) and/or the expression of cell adhesion molecules, with potential in the treatment of arthritis, asthma, inflammatory bowel disease, sepsis, rhinitis, AIDS, cardiovascular disorders, psoriasis, thrombosis, cachexia, viral infections, gout, graft-versus-host disease and transplant rejection. Other specifically claimed pyridylpyrrole compounds include the following:



Compound	R1	R2	R3	Formula
261955	4-Pyr	Me	CF3	C ₁₇ H ₁₂ F ₃ N ₃ O
261956	-(CH2)3-		Me	C ₁₄ H ₁₄ N ₂ O
261957	4-F-Ph	Me	Me	C ₁₈ H ₁₅ FN ₂ O
261958	-CH2CH(Me)CH2-		Me	C ₁₅ H ₁₆ N ₂ O
261959	-C(Me)2CH2CH2-		Me	C ₁₆ H ₁₈ N ₂ O
261960	4-(CO2Me)-Ph	Me	Me	C ₂₀ H ₁₈ N ₂ O ₃
261961	4-Cl-Ph	Me	Me	C ₁₈ H ₁₅ ClN ₂ O
261962	4-morpholinyl	Me	Me	C ₁₆ H ₁₉ N ₃ O ₂

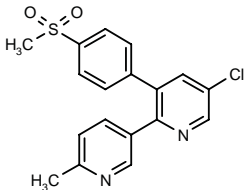
SOURCE – Pfizer.

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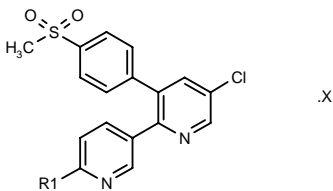
261533

5-Chloro-3-[4-(methylsulfonyl)phenyl]-2-(6-methylpyridin-3-yl)pyridine



C18-H15-Cl-N2-O2-S; Mol wt: 358.84

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor with an IC₅₀ value of 1.1 μM against COX-2 enzyme from whole blood and an IC₅₀ > 10 μM against COX-1 enzyme from U937 cell microsomes (selectivity ratio > 9.1). Antiinflammatory activity was assessed *in vivo* by measuring inhibition of carrageenan-induced rat paw edema (ED₅₀ = 0.6 mg/kg p.o.). Within this series of specifically claimed substituted pyridines, the following are also included:



Compound	R1	X	Formula
262138	H		C ₁₇ H ₁₃ ClN ₂ O ₂ S
262139	H	MeSO3H	C ₁₇ H ₁₃ ClN ₂ O ₂ S.CH ₄ O ₃ S
262140	H	HCl	C ₁₇ H ₁₃ ClN ₂ O ₂ S.HCl
262141	Et		C ₁₉ H ₁₇ ClN ₂ O ₂ S
262142	Et	MeSO3H	C ₁₉ H ₁₇ ClN ₂ O ₂ S.CH ₄ O ₃ S

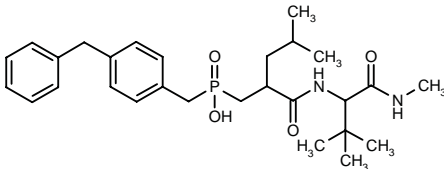
SOURCE – Merck Frosst.

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1. Dube, D. et al. (Merck Frosst Canada, Inc.) *Substd. pyridines as selective cyclooxygenase-2 inhibitors*. WO 9803484.

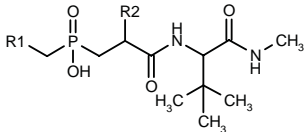
261549

(4-Benzylbenzyl)[2-[N-[2,2-dimethyl-1-(N-methyl-carbamoyl)propyl]carbamoyl]-4-methylpentyl]phosphinic acid

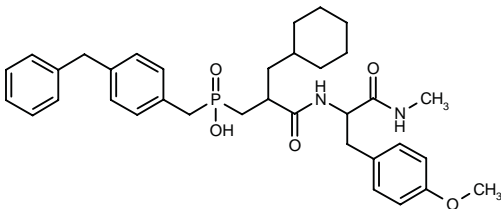


C28-H41-N2-O4-P; Mol wt: 500.62

ACTION – Inhibitor of matrix metalloproteinases (MMPs) and/or the production of tumor necrosis factor (TNF), with potential in the treatment of diseases where MMPs and/or TNF are involved such as arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, AIDS and septic shock. Other specifically claimed compounds from this series of phosphinic acid-based inhibitors include the following:



Compound	R1	R2	Formula
262228	4-(3-F-PhCH2)-Ph	i-Bu	C ₂₈ H ₄₀ FN ₂ O ₄ P
262230	4-(cyclohexyl-CH2)-Ph	i-Bu	C ₂₈ H ₄₇ N ₂ O ₄ P
262231	4-(2-F-PhCH2)-Ph	i-Bu	C ₂₈ H ₄₀ FN ₂ O ₄ P
262232	4-(2-Cl-PhCH2)-Ph	i-Bu	C ₂₈ H ₄₀ ClN ₂ O ₄ P
262233	5-(PhCH2)-2-Pyr	i-Bu	C ₂₇ H ₄₀ N ₃ O ₄ P
262234	4-(2-F-PhCH2)-Ph	CH2CH2CF3	C ₂₇ H ₃₅ F ₄ N ₂ O ₄ P
262235	5-(PhCH2)-2-thienyl	i-Bu	C ₂₆ H ₃₉ N ₂ O ₄ PS



262229: C35-H45-N2-O5-P

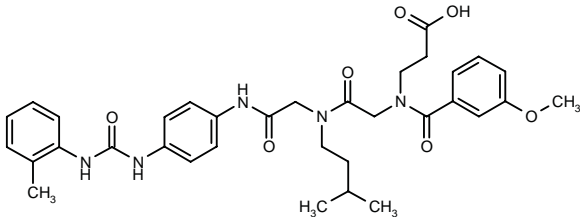
SOURCE – Pfizer.

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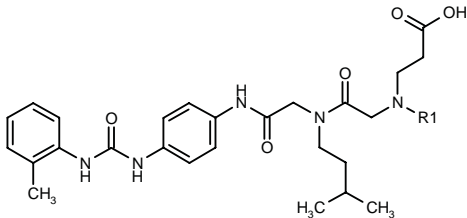
261554

N-(3-Methoxybenzoyl)-N-[N-(3-methylbutyl)-N-[N-[4-[3-(2-methylphenyl)ureido]phenyl]carbamoylmethyl]carbamoyl-methyl]-β-alanine



C34-H41-N5-O7; Mol wt: 631.73

ACTION – Cell adhesion inhibitor particularly active in inhibiting the binding of ligands to the α4β1 integrin (also known as VLA-4, or very late antigen of activation-4, and CD49d/CD20). The compound has an integrin scaffold derived from a compound with inhibitory activity against fibrinogen (gpIIb/IIIa); the gpIIb/IIIa specificity determinant is removed and replaced with a VLA-4 specificity determinant. Potentially useful for the treatment of inflammatory and immune disorders such as arthritis, asthma, adult respiratory distress syndrome, multiple sclerosis and diabetes. Other preferred compounds include the following:



Compound	R1	Formula
262502	SO2Me	C ₂₇ H ₃₇ N ₅ O ₇ S
262503	2-furyl-CO	C ₃₁ H ₃₇ N ₅ O ₇
262504	COCH2CH2CO2Me	C ₃₁ H ₄₁ N ₅ O ₈
262505	COPh	C ₃₃ H ₃₉ N ₅ O ₆
262506	3-furyl-CO	C ₃₁ H ₃₇ N ₅ O ₇

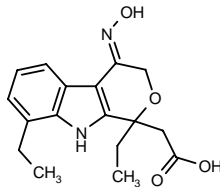
SOURCE – Biogen.

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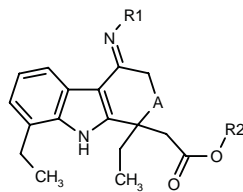
261571

2-[1,8-Diethyl-4-(hydroxyimino)-1,3,4,9-tetrahydro-pyrano[3,4-*b*]indol-1-yl]acetic acid



C17-H20-N2-O4; Mol wt: 316.36

ACTION – Agent for the treatment of arthritis, colorectal cancer and Alzheimer’s disease that acts by inhibiting cyclooxygenase type 2 (COX-2), affording 50% inhibition of human COX-2 cloned from human monocytes at 3.3 μM and 96% inhibition of COX-1 at 90 μM. Other specifically claimed pyranoidole and carbazole derivatives include the following:



Compound	R1	R2	A	Formula
262500	NHSO2Me	Na	O	C ₁₈ H ₂₂ N ₃ NaO ₅ S
262501	OH	H	CH2	C ₁₈ H ₂₂ N ₂ O ₃

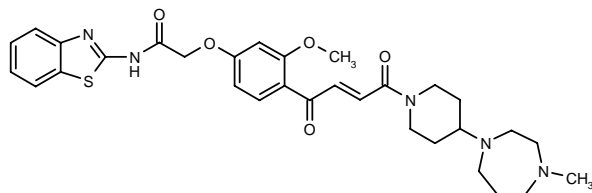
SOURCE – American Home Products.

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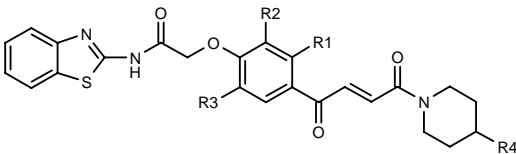
261574

N-(2-Benzothiazolyl)-2-[3-methoxy-4-[4-[4-(4-methyl-perhydro-1,4-diazepin-1-yl)piperidin-1-yl]fumaroyl]-phenoxy]acetamide

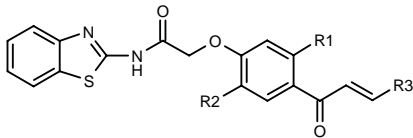


C31-H37-N5-O5-S; Mol wt: 591.72

ACTION – Agent for the treatment of autoimmune, immune, allergic, inflammatory and ischemic disorders such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, asthma, Crohn’s disease, atopic dermatitis, graft-vs.-host disease and acute pancreatitis that acts by inhibition of protein kinase C (IC₅₀ = 0.08 μM using enzyme purified from rat brain). It was active at doses of 30-50 mg/kg p.o. in a mouse collagen-induced arthritis model and in a mouse chronic graft-vs.-host disease model. It was also active in a model of atopic dermatitis in mice when applied in a concentration of 0.75% 30 min before and after the application of TNCB (1% trinitrobenzene). Other specifically claimed thiazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
262639	OMe	H	Et	4-Me-perhydro-1,4-diazepin-1-yl	C ₃₃ H ₄₁ N ₅ O ₅ S
262640	H	i-Pr	H	4-Me-1-Piz	C ₃₂ H ₃₉ N ₅ O ₄ S
262642	H	H	OEt	4-Me-1-Piz	C ₃₁ H ₃₇ N ₅ O ₅ S
262643	Me	H	H	4-Me-perhydro-1,4-diazepin-1-yl	C ₃₁ H ₃₇ N ₅ O ₄ S
263225	H	OMe	H	4-Me-1-Piz	C ₃₀ H ₃₆ N ₅ O ₅ S
263226	Me	Me	H	4-Me-perhydro-1,4-diazepin-1-yl	C ₃₂ H ₃₉ N ₅ O ₄ S
263227	OMe	H	H	3,4-(Me)2-1-Piz	C ₃₁ H ₃₇ N ₅ O ₅ S
263229	H	OMe	H	4-Me-perhydro-1,4-diazepin-1-yl	C ₃₁ H ₃₇ N ₅ O ₅ S
263230	H	Bu	H	4-Me-perhydro-1,4-diazepin-1-yl	C ₃₄ H ₄₃ N ₅ O ₄ S



Compound	R1	R2	R3	Formula
262641	H	OMe	2-(4-Me-1-Piz-CH2)-4-morpholinyl-CO	C ₃₀ H ₃₆ N ₅ O ₆ S
262644	OMe	Et	4-Me-1-Piz	C ₂₈ H ₃₀ N ₄ O ₄ S
262645	H	CF3	4-OH-1-Piz	C ₂₃ H ₂₁ F ₃ N ₄ O ₄ S
263224	H	F	2-(4-Me-1-Piz-CH2)-4-morpholinyl-CO	C ₂₉ H ₃₂ N ₅ O ₅ S
263228	OMe	i-Pr	4-Me-1-Piz-CO	C ₂₈ H ₃₂ N ₄ O ₅ S

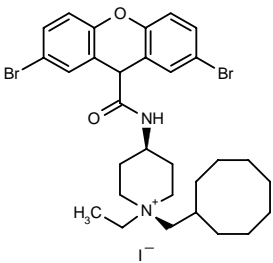
SOURCE – Otsuka.

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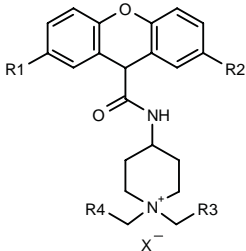
261585

cis-1-(Cyclooctylmethyl)-4-(2,7-dibromoxanthen-9-ylcarboxamido)-1-ethylpiperidinium iodide

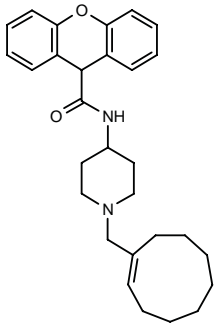


C30-H39-Br2-I-N2-O2; Mol wt: 746.36

ACTION – Agent for the treatment of acute and chronic inflammatory disorders, AIDS, cancer, ischemia/reperfusion disorders and arteriosclerosis, a chemokine receptor antagonist, as demonstrated in binding assays by inhibition of [¹²⁵I]-MIP-1 α and [¹²⁵I]-eotaxin binding to human CCR1 and CCR3 receptors, respectively, expressed in CHO cells (IC₅₀ = 1.9 and 2.7 nM, respectively). Additionally, compound inhibited the eotaxin-induced increase in Ca²⁺ concentrations in human eosinophils expressing the CCR3 receptor (51% inhibition at a concentration of 41 nM). Other related compounds include the following:



Compound	R1=R2	R3	R4	X	Isomer	Formula
262730	Cl	1-cycloheptenyl	Me	I ⁻	cis	C ₃₀ H ₃₇ Cl ₂ N ₂ O ₂
262731	H	cyclooctyl	Me	I ⁻		C ₃₀ H ₄₁ IN ₂ O ₂
262732	Br	cyclooctyl	H	I ⁻		C ₂₉ H ₃₇ Br ₂ N ₂ O ₂
262734	Cl	1-cycloheptenyl	Me	Br ⁻	cis	C ₃₀ H ₃₇ BrCl ₂ N ₂ O ₂



262733: C₂₉-H₃₆-N₂-O₂

SOURCE – Banyu.

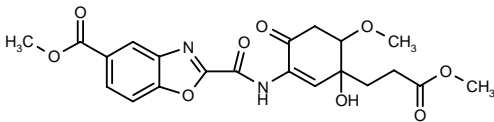
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AI-071

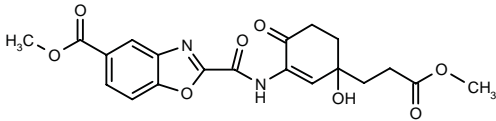
261875

2-[N-[3-Hydroxy-4-methoxy-3-[2-(methoxycarbonyl)ethyl]-6-oxo-1-cyclohexenyl]carbamoyl]benzoxazole-5-carboxylic acid methyl ester

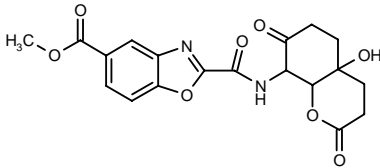


C₂₁-H₂₂-N₂-O₉; Mol wt: 446.41

ACTION – Antiinflammatory, antiarthritic and antiasthmatic agent isolated from *Microtetraspora spiralis* TA-0294 (FERM P-15757) that acts by inhibiting the action of endothelial leukocyte adhesion molecule-1 (ELAM-1). *In vitro*, it produced 75.9% inhibition of tumor necrosis factor- α (TNF- α)-stimulated adhesion of Colo-201 cancer cells to human umbilical vein endothelial cells (HUVEC) at 30 μ g/ml. Other compounds isolated from the same source include the following:



AI-070 [262934]: C₂₀-H₂₀-N₂-O₈



AI-072 [262935]: C₁₉-H₁₈-N₂-O₈

SOURCE – Taisho.

REFERENCES

1. Sugawara, K. et al. (Taisho Pharm. Co., Ltd.) *Benzoxazoles*. JP 98045731.

IMMUNOLOGIC DRUGS

262182

Polynucleotide tuberculosis vaccine

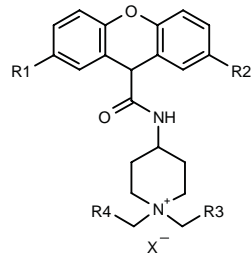
ACTION – Polynucleotide tuberculosis vaccine that provides immune protection against infection by *Mycobacterium tuberculosis* or *Mycobacterium bovis*, comprising a plasmid vector comprising a nucleotide sequence encoding antigen 85A linked to transcription regulatory elements such as the cytomegalovirus promoter with the Intron A sequence and the bovine growth hormone terminator. Protective efficacy was demonstrated in mice after challenge with *M. bovis* BCG, as measured by a reduction in mycobacterial multiplication in the spleens and lungs of vaccinated mice compared to the control group.

SOURCE – Merck & Co.

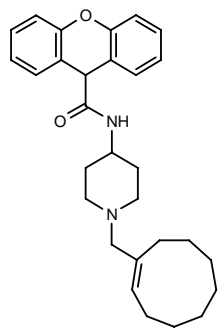
REFERENCES

1. Content, J. et al. (Merck & Co., Inc.) *Polynucleotide tuberculosis vaccine*. US 5736524.

ACTION – Agent for the treatment of acute and chronic inflammatory disorders, AIDS, cancer, ischemia/reperfusion disorders and arteriosclerosis, a chemokine receptor antagonist, as demonstrated in binding assays by inhibition of [¹²⁵I]-MIP-1 α and [¹²⁵I]-eotaxin binding to human CCR1 and CCR3 receptors, respectively, expressed in CHO cells (IC₅₀ = 1.9 and 2.7 nM, respectively). Additionally, compound inhibited the eotaxin-induced increase in Ca²⁺ concentrations in human eosinophils expressing the CCR3 receptor (51% inhibition at a concentration of 41 nM). Other related compounds include the following:



Compound	R1=R2	R3	R4	X	Isomer	Formula
262730	Cl	1-cycloheptenyl	Me	I ⁻	cis	C ₃₀ H ₃₇ Cl ₂ N ₂ O ₂
262731	H	cyclooctyl	Me	I ⁻		C ₃₀ H ₄₁ IN ₂ O ₂
262732	Br	cyclooctyl	H	I ⁻		C ₂₉ H ₃₇ Br ₂ N ₂ O ₂
262734	Cl	1-cycloheptenyl	Me	Br ⁻	cis	C ₃₀ H ₃₇ BrCl ₂ N ₂ O ₂



262733: C₂₉-H₃₆-N₂-O₂

SOURCE – Banyu.

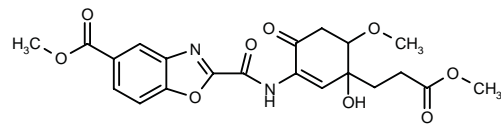
REFERENCES

1. Naya, A. et al. (Banyu Pharm. Co., Ltd.) *Chemokine receptor antagonists*. WO 9804554.

AI-071

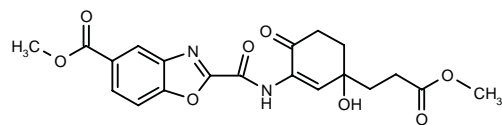
261875

2-[N-[3-Hydroxy-4-methoxy-3-[2-(methoxycarbonyl)ethyl]-6-oxo-1-cyclohexenyl]carbamoyl]benzoxazole-5-carboxylic acid methyl ester

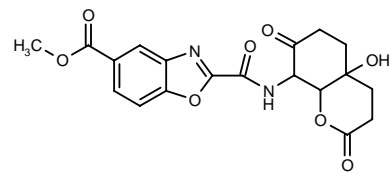


C₂₁-H₂₂-N₂-O₉; Mol wt: 446.41

ACTION – Antiinflammatory, antiarthritic and antiasthmatic agent isolated from *Microtetraspora spiralis* TA-0294 (FERM P-15757) that acts by inhibiting the action of endothelial leukocyte adhesion molecule-1 (ELAM-1). *In vitro*, it produced 75.9% inhibition of tumor necrosis factor- α (TNF- α)-stimulated adhesion of Colo-201 cancer cells to human umbilical vein endothelial cells (HUVEC) at 30 μ g/ml. Other compounds isolated from the same source include the following:



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AI-072 [262935]: C₁₉-H₁₈-N₂-O₈

SOURCE – Taisho.

REFERENCES

1. Sugawara, K. et al. (Taisho Pharm. Co., Ltd.) *Benzoxazoles*. JP 98045731.

IMMUNOLOGIC DRUGS

262182

Polynucleotide tuberculosis vaccine

ACTION – Polynucleotide tuberculosis vaccine that provides immune protection against infection by *Mycobacterium tuberculosis* or *Mycobacterium bovis*, comprising a plasmid vector comprising a nucleotide sequence encoding antigen 85A linked to transcription regulatory elements such as the cytomegalovirus promoter with the Intron A sequence and the bovine growth hormone terminator. Protective efficacy was demonstrated in mice after challenge with *M. bovis* BCG, as measured by a reduction in mycobacterial multiplication in the spleens and lungs of vaccinated mice compared to the control group.

SOURCE – Merck & Co.

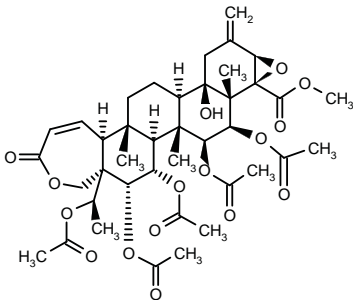
REFERENCES

1. Content, J. et al. (Merck & Co., Inc.) *Polynucleotide tuberculosis vaccine*. US 5736524.

L-755860*

246724

[1aS-(1aα,1bβ,2β,3β,3aβ,3bα,4α,5α,5aα,10aα,10bβ,12aα,12bβ,14aα)]-2,3,4,5-Tetraacetoxy-5a-[1(*R*)-acetoxyethyl]-12b-hydroxy-1b,3a,10b-trimethyl-14,14-methylene-8-oxo-1a,1b,2,3,3a,3b,4,5,5a,6,8,10a,11,12,12a,12b,13,14,14a-icosahydrooxireno[7,8]chryseno-[2,1-*c*]oxepin-1a-carboxylic acid methyl ester



C40-H52-O16; Mol wt: 788.84

ACTION – Immunosuppressive agent, a highly funtionalized triterpenoid isolated from the root of *Spachea correa* that acts as a potent blocker of the Kv1.3 channel in human T-cells.

SOURCE – Merck & Co.

REFERENCES

1. Goetz, M.A. (Merck & Co., Inc.) *Triterpenes*. US 5631282.

2. Baker, R.K. et al. *Chemistry of L-755,860 - A nor-triterpenoid from Spachea correa; Part I*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst ORGN 066.

3. Bao, J. et al. *Chemistry of L-755,860 - A nor-triterpenoid from Spachea correa; Part III*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst ORGN 068.

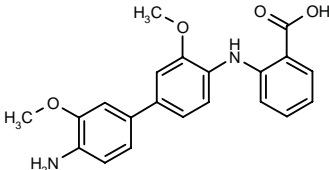
4. Kayser, F. et al. *Chemistry of L-755,860 - A nor-triterpenoid from Spachea correa; Part II*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst ORGN 067.

*Identified compound **246724** Drug Data Rep 1997, 19(5): 454.

PRO-3249

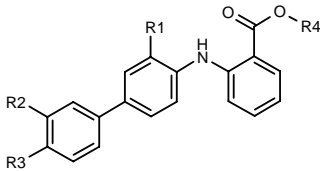
262350

2-(4'-Amino-3,3'-dimethoxybiphenyl-4-ylamino)benzoic acid



C21-H20-N2-O4; Mol wt: 364.40

ACTION – Immunosuppressant useful for preventing or reducing graft rejection in organ and bone marrow transplantation, as well as T-lymphocyte-mediated autoimmune diseases such as diabetes, rheumatoid arthritis and psoriasis. It inhibited thymidine incorporation in an antigen-specific peripheral blood lymphocyte (PBL) proliferation assay with an IC₅₀ of 5 ng/ml. Within this series of aromatic compounds, the following are also included:



Compound	R1=R2	R3	R4	Formula
PRO-4323 [262445]	OMe	t-BuOCONH	H	C ₂₆ H ₂₈ N ₂ O ₆
PRO-4403 [262446]	OMe	H	H	C ₂₁ H ₁₉ NO ₄
PRO-6370 [262447]	OMe	NHMe	H	C ₂₂ H ₂₂ N ₂ O ₄
PRO-4402 [262448]	OMe	Br	H	C ₂₁ H ₁₈ BrNO ₄
PRO-5021 [262449]	OMe	NH2	Me	C ₂₂ H ₂₂ N ₂ O ₄
PRO-4916 [262450]	H	NH2	H	C ₁₉ H ₁₈ N ₂ O ₂

SOURCE – Procept.

REFERENCES

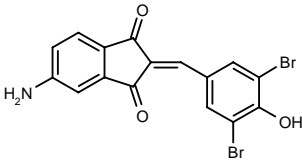
1. Ocain, T.D. et al. (Procept, Inc.) *Aromatic cpds. for inhibiting immune response*. US 5739169.

RWJ-64777

262292

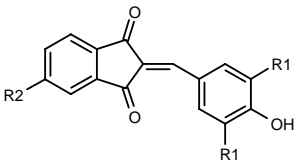
5-Amino-2(*Z*)-(3,5-dibromo-4-hydroxybenzylidene)-indane-1,3-dione

R-64777



C16-H9-Br2-N-O3; Mol wt: 423.06

ACTION – Potent and selective inhibitor of p56^{lck} tyrosine kinase (IC₅₀ = 32 nM), which is primarily expressed in T- and NK cells and is known to play a crucial role in their proliferative and effector functions. Other related compounds include the following:



Compound	R1	R2	Formula
R-63631 [262293] RWJ-63631	Br	OMe	C ₁₇ H ₁₆ Br ₂ O ₄
R-65012 [262294] RWJ-65012	Cl	NH2	C ₁₆ H ₉ Cl ₂ NO ₃

It is expected that inhibition of p56^{lck} tyrosine kinase may produce inhibition of immune responses with minimal toxic effects outside the immune system.

SOURCE – R.W. Johnson.

REFERENCES

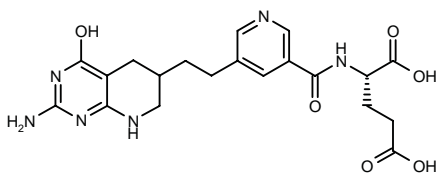
1. Rupert, K.C. et al. *The development of novel and selective p56 Lck tyrosine kinase inhibitors*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 170.

ONCOLYTIC DRUGS

ANTIMETABOLITES

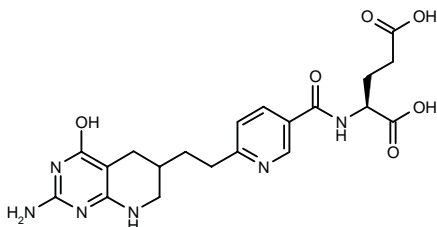
260195

N-[5-[2-(2-Amino-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)ethyl]pyridin-3-ylcarbonyl]-L-glutamic acid

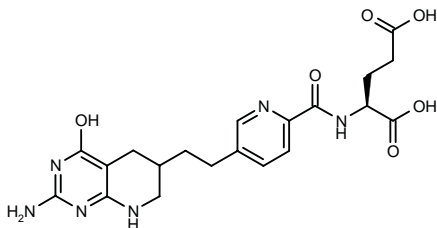


C20-H24-N6-O6; Mol wt: 444.45

ACTION – Antineoplastic agent that acts by inhibiting enzymes which utilize folic acid as a substrate such as glycinamide ribonucleotide formyltransferase (phosphoribosylglycinamide formyltransferase; $K_i = 0.126 \mu\text{M}$), dihydrofolate reductase and thymidylate synthase. *In vitro*, it inhibited the growth of human lymphoblastic leukemia CCRF-CEM cells with an IC_{50} value of $0.1 \mu\text{g/ml}$. Other specifically claimed compounds from this series of 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines include the following:



262653: C20-H24-N6-O6



262654: C20-H24-N6-O6

SOURCE – Princeton Univ., Princeton, NJ (US).

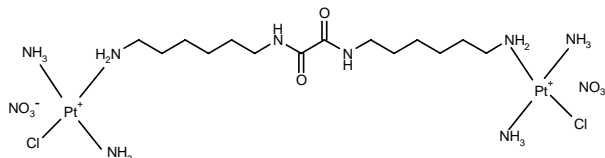
REFERENCES

1. Taylor, E.C. and Gillespie, P. (Trustees Princeton Univ.) 5,6,7,8-Tetrahydropyrido[2,3-*d*]pyrimidine derivs. WO 9749705.

DNA-DAMAGING DRUGS

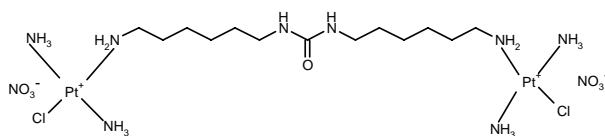
261550

[μ -*N,N'*-Bis(6-aminohexyl)oxamide]bis(*trans*-diamminechloroplatinum)(2+) dinitrate



C14-H42-Cl2-N10-O8-Pt2; Mol wt: 939.63

ACTION – Antineoplastic bisplatinum complex with potent cytotoxicity against murine leukemia L1210 and human ovarian carcinoma A2780 cells ($\text{IC}_{50} = 1.14$ and $0.68 \mu\text{g/ml}$, respectively, vs. 1.33 and $2.4 \mu\text{g/ml}$, respectively, for cisplatin), including cisplatin-resistant L1210 and A2780 sublines ($\text{IC}_{50} = 1.06$ and $2.15 \mu\text{g/ml}$, respectively, vs. 59 and $16.1 \mu\text{g/ml}$, respectively, for cisplatin). Compound is reported to be effective in L1210-bearing mice following i.p. administration. Another related bisplatinum complex is:



262222: C13-H42-Cl2-N10-O7-Pt2

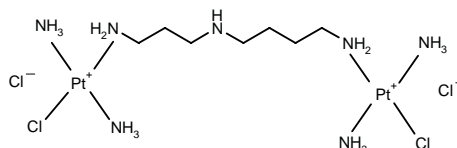
SOURCES – Boehringer Mannheim; Virginia Commonwealth Univ., Richmond, VA (US).

REFERENCES

1. Farrell, N.P. et al. (Boehringer Mannheim Italia SpA; Virginia Commonwealth Univ.) New bis-platinum complexes with polymethylene derivs. as ligands having antitumor activity. WO 9803518.

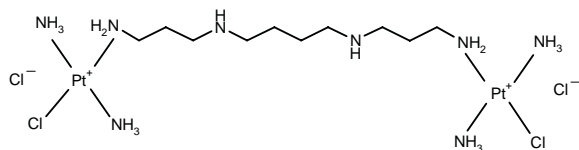
261551

[μ -*N*-(3-Aminopropyl)butane-1,4-diamine]bis(*trans*-diamminechloroplatinum)(2+) dichloride



C7-H31-Cl4-N4-Pt2; Mol wt: 745.36

ACTION – Antineoplastic bisplatinum complex with potent cytotoxicity against murine leukemia L1210 ($\text{IC}_{50} = 0.75$ and $0.41 \mu\text{g/ml}$ at 2 and 72 h, respectively, vs. 1.33 and $0.42 \mu\text{g/ml}$, respectively, for cisplatin) and human ovarian carcinoma A2780 cells ($\text{IC}_{50} < 0.005 \mu\text{g/ml}$ at 1 h vs. $2.4 \mu\text{g/ml}$ for cisplatin), as well as cisplatin-resistant L1210 and A2780 sublines ($\text{IC}_{50} = 0.03$ and $0.13 \mu\text{g/ml}$ at 72 and 1 h after treatment, respectively); additionally, compound exhibits a faster onset of action than cisplatin. Another related bisplatinum complex is:



262221: C10-H38-Cl4-N8-Pt2

SOURCES – Boehringer Mannheim; Virginia Commonwealth Univ., Richmond, VA (US).

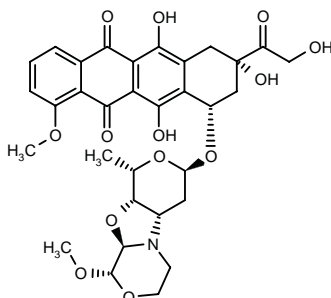
REFERENCES

1. Farrell, N.P. (Boehringer Mannheim Italia SpA; Virginia Commonwealth Univ.) *New bis-platinum complexes with polyamine ligands as antitumor agents*. WO 9803519.

ANTIBIOTICS AND ALKALOIDS

261228

[1S-(1 α ,3 β ,4 α ,9 α ,9 α ,10 α)]-10-O-(9-Methoxy-1-methylperhydropyrano[4',3':4,5]oxazolo[2,3-c][1,4]oxazin-3-yl)adriamycinone



C32-H35-N-O13; Mol wt: 641.63

ACTION – Antineoplastic agent, a specifically claimed compound within a series of morpholinyl anthracycline derivatives found to exhibit extremely potent *in vitro* cytotoxicity against L1210 leukemia cells.

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Caruso, M. et al. (Pharmacia & Upjohn SpA) *Morpholinyl anthracycline derivs*. WO 9802446.

FE35A

262833

C30-H31-N-O9 ; Mol wt: 549.58

ACTION – Antineoplastic agent isolated from *Streptomyces rochei* 3218-GM2 (FERM P-15720), with potent cytotoxicity against human ovarian cancer A2780 cells (IC₅₀ = 0.54 μ g/ml). Another compound from this source is:

FE35B [263067]: C31-H31-N-O10

SOURCE – Nippon Kayaku.

REFERENCES

1. Yamashita, N. and Seto, H. (Nippon Kayaku Co., Ltd.) *Novel cpds. FE35A and B, their preparation method and their use*. JP 98081692.

K-93-0711-R6

259192

ACTION – Antineoplastic antibiotic isolated from a culture of *Streptomyces* sp. (FERM P-15253), with potent *in vitro* cytotoxicity against murine leukemia P388, including the doxorubicin-resistant line P388/ADM (IC₅₀ = 0.08 and 0.07 μ g/ml, respectively, against sensitive and resistant cells). Another compound isolated from the same source is:

K-93-0711-R4 [261492]

SOURCE – Kitasato Inst., Tokyo (JP).

REFERENCES

1. Ohmura, S. et al. (Kitasato Inst.) *Novel antibiotics K93-0711-R4 and K93-0711-R6, and preparation method thereof*. JP 97315984.

NA-16887

261881

ACTION – Antineoplastic and antibacterial agent produced by culturing the microorganism *Actinomadura* sp. NA 16887 (FERM P-15400), with good antiproliferative activity against human ovarian cancer A2780 (IC₅₀ = 0.03 μ M) and colon cancer SW 480 cells (IC₅₀ = 0.05 μ M). Antibacterial activity was assessed *in vitro* against *Bacillus subtilis* IFO-3007 and *Staphylococcus aureus* FAD 209.

SOURCE – Nippon Kayaku.

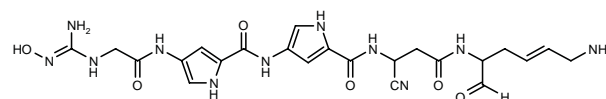
REFERENCES

1. Nishikiori, T. et al. (Nippon Kayaku Co., Ltd.) *Novel bioactive substance NA16887, preparation method thereof and their use*. JP 98045789.

UCH-15B

262126

N-[5-Amino-1-formyl-3(*E*)-pentenyl]-3-cyano-3-[4-[4-[2-(*N*²-hydroxyguanidino)acetamido]-1*H*-pyrrol-2-yl]-carboxamido]-1*H*-pyrrol-2-ylcarboxamido]propionamide



C23-H29-N11-O6; Mol wt: 555.55

ACTION – Antineoplastic antibiotic that binds to DNA without acting on topoisomerase, produced by a *Streptomyces* sp. It showed cytotoxic activity against HeLa S3 cells (IC₅₀ = 1.0 μ M) and significant antitumor activity against s.c. mouse sarcoma 180 (T/C = 44% at 0.38 mg/kg i.v.).

SOURCE – Kyowa Hakko.

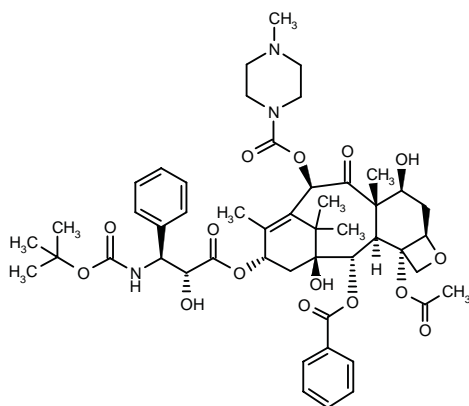
REFERENCES

1. Mizukami, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Cpds. UCH 15*. WO 9710208.
2. Asai, A. et al. *Study for novel antitumor antibiotics, UCH15B*. Nippon Nogekagaku Kaishi 1998, 72(3, Suppl.): Abst 2A10p13.

ANTIMITOTIC DRUGS

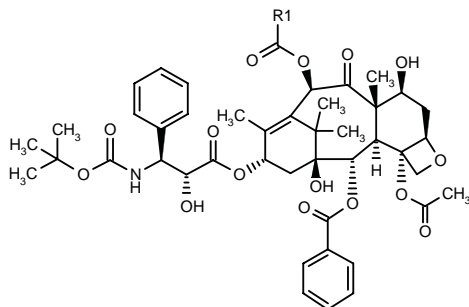
261217

[2a*R*]-[2a α ,4 β ,4a β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12a α ,12b α]]-12b-Acetoxy-9-[3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropionyloxy]-12-benzoyloxy-4,11-dihydroxy-4a,8,13,13-tetramethyl-6-(4-methylpiperazin-1-ylcarbonyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz-[1,2-*b*]oxet-5-one



C49-H63-N3-O15; Mol wt: 934.05

ACTION – Antineoplastic agent, a taxane derivative reported to possess excellent antitumor activity and high water solubility. Compound was more potent than paclitaxel in inhibiting the proliferation of KB cells (GI₅₀ = 0.59 ng/ml vs. 2.0 ng/ml for paclitaxel). Other related compounds include the following:



Compound	R1	Formula
262262	4-[N(Pr)2]-1-Pip	C ₅₅ H ₇₅ N ₃ O ₁₅
262263	4-(1-Pip)-1-Pip	C ₅₄ H ₇₁ N ₃ O ₁₅
262264	4-Et-1-Piz	C ₅₀ H ₆₅ N ₃ O ₁₅
262265	4-(i-PrNHCOCH2)-1-Piz	C ₅₃ H ₇₀ N ₄ O ₁₆

SOURCE – Yakult Honsha.

REFERENCES

1. Shimizu, H. et al. (Yakult Honsha Co., Ltd.) *Taxane derivs. and drugs containing the same*. WO 9802426.

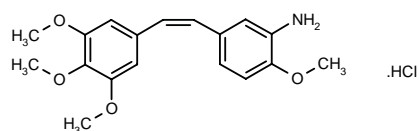
AC-7739^{*,2,3}

262290

221812 (as free base)

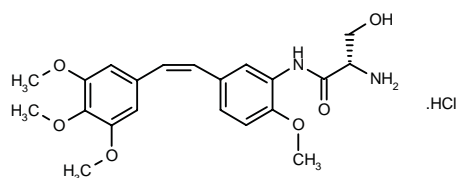
3-Amino-3',4,4',5'-tetramethoxy-*cis*-stilbene hydrochloride

2-Methoxy-5-[2(*Z*)-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine hydrochloride



C18-H21-N-O4.HCl; Mol wt: 351.83

ACTION – Antineoplastic agent, a combretastatin A-4 derivative shown to potently inhibit the growth of murine colon 26 adenocarcinoma cells (IC₅₀ = 5.1 nM) and tubulin polymerization (IC₅₀ = 4 μ M). It was active following i.v. administration against murine colon 26, colon 38 and 3LL tumors and human HCT-15 xenografts in mice, giving inhibition ratios (IR%) of 69 (40 mg/kg), 72 (10 mg/kg), 65 (40 mg/kg) and 53 (40 mg/kg), respectively, being more effective than cisplatin in the colon 38, 3LL and HCT-15 models and more effective than the parent compound in the colon 26 model. An amino acid prodrug with superior antitumor activity is:



262298^{1,3}: C21-H26-N2-O6.HCl

SOURCE – Ajinomoto.

REFERENCES

1. Hatanaka, T. et al. (Ajinomoto Co., Ltd.) *Stilbene derivs. and pharmaceutical compsns. containing them*. CA 2171275, EP 731085, JP 96301831, US 5674906.
2. Ohsumi, K. et al. (Ajinomoto Co., Inc.) *Cytotoxic stilbene derivs. and pharmaceutical compsns. containing them*. EP 641767, JP 95228558, US 5525632.
3. Ohsumi, K. et al. *(Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenylamine hydrochloride (AC-7739); a novel antitumor agent derived from combretastatin A-4*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 195.

*Identified compound 221812 Drug Data Rep 1995, 17(7): 674.

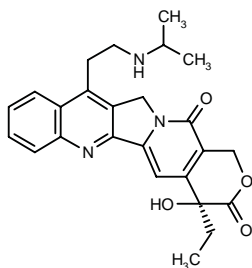
DNA-INTERCALATING DRUGS

CKD-602*

239803

4(S)-Ethyl-4-hydroxy-11-[2-(isopropylamino)ethyl]-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]-quinoline-3,14-dione

(20S)-7-[2-(Isopropylamino)ethyl]camptothecin



C25-H27-N3-O4; Mol wt: 433.51

ACTION – Antineoplastic agent, a water-soluble camptothecin analog with broad-spectrum activity against human tumor cell lines at least equivalent to that of camptothecin and topotecan. Although it was somewhat less active than camptothecin against murine leukemia L1210 *in vitro* (IC_{50} = 0.55 μ g/ml vs. 0.2 μ g/ml), it was more active *in vivo*, giving an ILS of 168% vs. 110% for camptothecin; it was also more active *in vivo* than topotecan against leukemia L1210 (ILS = 168% vs. 127%), murine leukemia P388, Lewis lung carcinoma, melanoma B16 and colon cancer CX-1. It was more active and had a broader therapeutic dose range than topotecan against a panel of human colon and breast carcinoma xenografts.

SOURCE – Chong Kun Dang.

REFERENCES

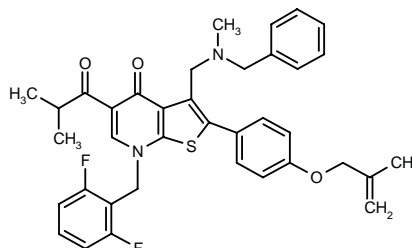
1. Jew, S.S. et al. (Chong Kun Dang Corp.) *Camptothecin derivs. and its manufacturing method*. EP 802915, WO 9621666.
2. Jew, S. et al. *Synthesis and antitumor activity of 7-substituted and 20-substituted camptothecin analogues*. AFMC Int Med Chem Symp (July 27-Aug 1, Seoul) 1997, Abst PB-55.
3. Lee, J.H. et al. *Antitumor activities of CKD602, a novel camptothecin derivative*. Proc Amer Assoc Cancer Res 1998, 39: Abst 2071.
4. Lee, J.H. et al. *Pharmacokinetics and antitumor activity of a novel camptothecin compound, CKD602, as determined by ex vivo pharmacodynamics*. Proc Amer Assoc Cancer Res 1998, 39: Abst 3544.

*Identified compound **239803** Drug Data Rep 1996, 18(11): 1022.

HORMONAL AGENTS

261855

3-(N-Benzyl-N-methylaminomethyl)-2-[4-(2-methyl-2-propenyloxy)phenyl]-7-(2,6-difluorobenzyl)-5-isobutyryl-thieno[2,3-b]pyridin-4(7H)-one



C37-H36-F2-N2-O3-S; Mol wt: 626.76

ACTION – Agent for the treatment of sex hormone-dependent disorders such as prostate cancer, breast cancer, endometriosis and precocious puberty, as well as for controlling fertility, that displays potent gonadotropin-releasing hormone (GnRH)-antagonist activity (IC_{50} = 10 nM against [125 I]-leuporelin binding to the human GnRH receptor expressed in CHO cells).

SOURCE – Takeda.

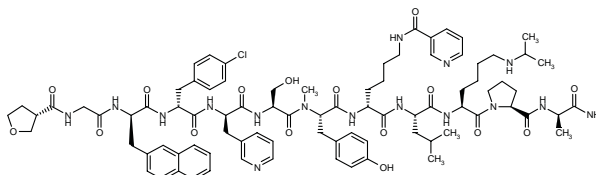
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A-84861

261731

Tetrahydrofuran-2(S)-ylcarbonyl-glycyl-D-(2-naphthyl)-alanyl-D-(4-chloro)phenylalanyl-D-(3-pyridyl)alanyl-L-seryl-L-(N-methyl)tyrosyl-D-[N⁶-(3-pyridylcarbonyl)]lysyl-L-leucyl-L-(N⁶-isopropyl)lysyl-L-prolyl-D-alaninamide



C85-H111-Cl-N16-O16; Mol wt: 1648.36

ACTION – Luteinizing hormone-releasing hormone (LHRH) antagonist potentially useful for the treatment of prostatic carcinoma and other hormone-dependent disorders. It has been selected for clinical studies on the basis of its equivalent *in vitro* and *in vivo* potency and significantly reduced tendency to induce histamine release from rat peritoneal mast cells compared to the parent compound A-75998.

SOURCES – Abbott; TAP.

REFERENCES

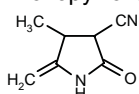
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2. Haviv, F. et al. *A-84861 a potent antagonist of luteinizing hormone-releasing hormone (LHRH) with reduced histamine release property*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 054.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

255657

4-Methyl-5-methylene-2-oxopyrrolidine-3-carbonitrile



C7-H8-N2-O; Mol wt: 136.15

ACTION – Antineoplastic agent, also claimed for use as an immunosuppressant and antidiabetic agent, an inhibitor of protein phosphatase (phosphoprotein phosphatase; IC₅₀ = 26 μM against human enzyme).

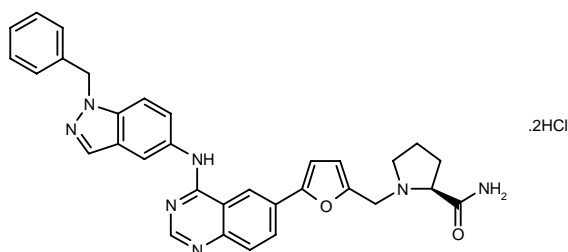
SOURCE – Taisho.

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1. Arai, K. and Sato, M. (Taisho Pharm. Co., Ltd.) *Pyrrolidone derivs*. JP 97295968, WO 9732847.

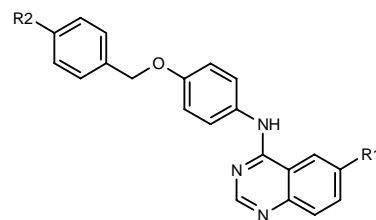
261221

1-[5-[4-(1-Benzyl-1*H*-indazol-5-ylamino)quinazolin-6-yl]-furan-2-ylmethyl]-L-prolinamide dihydrochloride

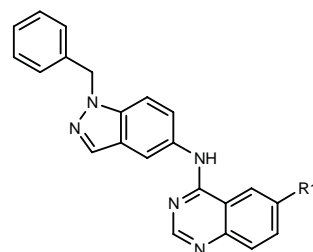


C32-H29-N7-O2.2HCl; Mol wt: 616.55

ACTION – Antineoplastic agent, a potent inhibitor of protein tyrosine kinases, particularly c-erbB-2 (IC₅₀ = 45 nM) and c-erbB-4 (IC₅₀ = 34 nM) protein tyrosine kinases. Compound inhibited the growth of human breast epithelial HB4a cells transformed by overexpression of c-erbB-2 (IC₅₀ = 9 nM) but had no effect on the growth of HB4a cells transfected with *ras* (IC₅₀ > 50,000 nM). Antiproliferative activity was also demonstrated against naturally occurring epidermal growth factor (EGF) receptor- or c-erbB-2-overexpressing human tumor cell lines such as breast BT474 (IC₅₀ = 2 nM), gastric N87 (IC₅₀ = 180 nM), lung Calu3 (IC₅₀ = 360 nM) and head and neck HN5 (IC₅₀ = 840 nM) cell lines. Also claimed for the treatment of psoriasis. Within this series of fused heterocyclic compounds, the following are also specifically claimed:



Compound	R1	R2	Formula
261942	2-furyl	H	C ₂₅ H ₁₉ N ₃ O ₂
261943	1-Me-5-imidazolyl	H	C ₂₅ H ₂₁ N ₅ O
261944	5-Me-1,3,4-oxadiazol-2-yl	F	C ₂₄ H ₁₈ FN ₃ O ₂
261946	5-Me-1,2,4-oxadiazol-3-yl	H	C ₂₄ H ₁₉ N ₃ O ₂
261947	5-(4-Me-1-Piz-CH2)-2-furyl	H	C ₃₁ H ₃₁ N ₃ O ₂
261948	5-[2(S)-(CONH2)-1-pyrrolidinyl-CH2]-2-furyl	H	C ₃₁ H ₂₉ N ₅ O ₃
261950	5-[MeSO2CH2CH2N(Me)CH2]-2-furyl	H	C ₃₀ H ₃₀ N ₄ O ₄ S
261951	5-(MeSO2CH2CH2NHCH2)-2-furyl	H	C ₂₉ H ₂₉ N ₅ O ₄ S



Compound	R1	Formula
261945	5-Me-1,2,4-triazol-3-yl	C ₂₅ H ₂₀ N ₈
261949	5-(MeSO2CH2CH2NHCH2)-2-furyl	C ₃₀ H ₂₈ N ₆ O ₃ S
261952	5-(4-oxo-1-Pip-CH2)-1,2,4-oxadiazol-3-yl	C ₃₀ H ₂₆ N ₈ O ₂
261953	5-(2-oxo-1-pyrrolidinyl-CH2)-1,2,4-oxadiazol-3-yl	C ₂₉ H ₂₄ N ₈ O ₂

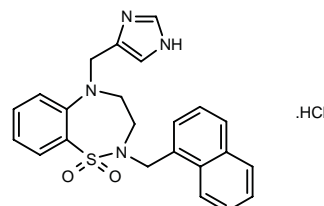
SOURCE – Glaxo Wellcome.

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1. Cockerill, G.S. et al. (Glaxo Group Ltd.) *Fused heterocyclic cpds. as protein tyrosine kinase inhibitors*. WO 9802434.

261223

5-(1*H*-Imidazol-4-ylmethyl)-2-(1-naphthylmethyl)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine 1,1-dioxide hydrochloride



C23-H22-N4-O2-S.HCl; Mol wt: 454.97

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and Ras protein farnesylation. It may also act as an inhibitor of other prenyl transferases such as geranylgeranyltransferase, and thus may also be useful against hepatitis delta virus infections. Other specifically claimed compounds within this series of thiadioxobenzodiazepines include the following:



Compound	R1	R2	R3	Formula
262550	H	H	CH2Ph	C ₂₀ H ₂₂ N ₄ O ₂ S.HCl
262551	H	Br	CH2Ph	C ₂₀ H ₂₁ BrN ₄ O ₂ S.HCl
262552	H	Ph	CH2Ph	C ₂₈ H ₂₆ N ₄ O ₂ S.HCl
262553	cyclohexyl-CONH	H	CH2Ph	C ₂₇ H ₃₃ N ₅ O ₃ S.HCl
262554	H	H	Ph	C ₁₉ H ₂₀ N ₄ O ₂ S.HCl

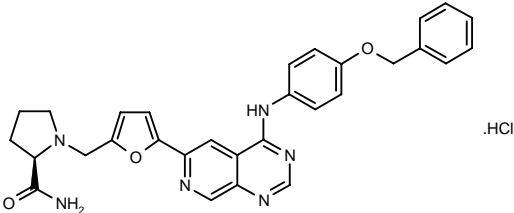
SOURCE – Bristol-Myers Squibb.

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1. Ding, C.Z. (Bristol-Myers Squibb Co.) *Thiadioxobenzodiazepine inhibitors of farnesyl protein transferase*. WO 9802436.

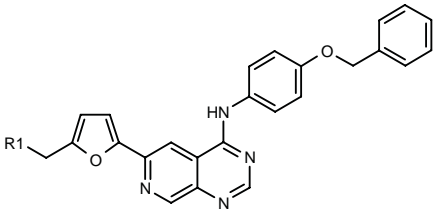
261224

1-[5-[4-(4-Benzyloxyphenylamino)pyrido[3,4-*d*]pyrimidin-6-yl]furan-2-ylmethyl]pyrrolidine-2(*R*)-carboxamide hydrochloride



C30-H28-N6-O3.HCl; Mol wt: 557.05

ACTION – Antineoplastic and antipsoriatic agent, a potent inhibitor of protein tyrosine kinases, particularly erbB-2 protein tyrosine kinase (IC₅₀ = 14 nM). Compound inhibited the growth of human breast epithelial HB4a cells transformed by overexpression of c-erbB-2 (IC₅₀ = 170 nM), without having a significant inhibitory effect on the growth of *ras*-transfected HB4a cells (IC₅₀ > 50,000 nM). Antiproliferative activity was also demonstrated against human head and neck cancer HN5 cells (IC₅₀ = 350 nM). Other specifically claimed compounds within this series of bicyclic heteroaromatic derivatives include the following:



Compound	R1	Formula
262015	NHCH2CH2SO2Me	C ₂₈ H ₂₇ N ₅ O ₄ S
262016	2(S)-(CONH2)-1-pyrrolidinyl	C ₃₀ H ₂₈ N ₆ O ₃
262017	2(S)-[CON(Me)2]-1-pyrrolidinyl	C ₃₂ H ₃₂ N ₆ O ₃

Other compounds in the series also inhibit epidermal growth factor (EGF) receptor tyrosine kinase.

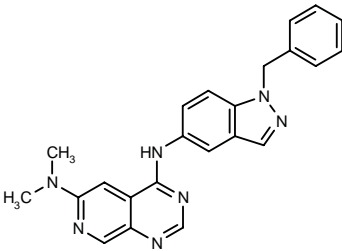
SOURCE – Glaxo Wellcome.

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1. Cockerill, G.S. et al. (Glaxo Group, Ltd.) *Bicyclic heteroaromatic cpds. as protein tyrosine kinase inhibitors*. WO 9802437.

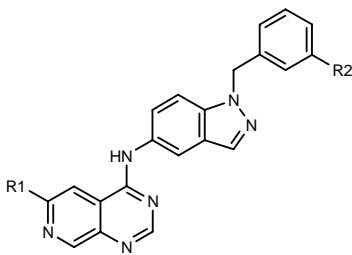
261225

*N*⁴-(1-Benzyl-1 *H*-indazol-5-yl)-*N*⁶,*N*⁶-dimethylpyrido[3,4-*d*]pyrimidine-4,6-diamine



C23-H21-N7; Mol wt: 395.47

ACTION – Antineoplastic agent, a potent inhibitor of protein tyrosine kinases, particularly epidermal growth factor (EGF) receptor (IC₅₀ = 1 nM), c-erbB-2 (IC₅₀ = 19 nM) and c-erbB-4 (IC₅₀ = 20 nM) protein tyrosine kinases. Compound inhibited the growth of human breast epithelial HB4a cells transformed by overexpression of c-erbB-2 (IC₅₀ = 110 nM) but had no significant inhibitory effect on the growth of HB4a cells transfected with *ras* (IC₅₀ = 17,000 nM). Antiproliferative activity was also demonstrated against naturally occurring EGF receptor- or c-erbB-2-overexpressing human tumor cell lines such as breast BT474 (IC₅₀ = 140 nM), head and neck HN5 (IC₅₀ = 300 nM), gastric N87 (IC₅₀ = 240 nM) and lung Calu3 (IC₅₀ = 380 nM) cell lines. Also claimed for the treatment of psoriasis. Within this series of bicyclic heteroaromatic compounds, the following are also specifically claimed:



Compound	R1	R2	Formula
262011	N(Me)2	F	C ₂₃ H ₂₀ FN ₇
262012	N(Me)Et	H	C ₂₄ H ₂₃ N ₇
262013	5-(MeSO2CH2CH2NHCH2)-2-furyl	H	C ₂₉ H ₂₇ N ₇ O ₃ S
262014	NHMe	H	C ₂₂ H ₁₉ N ₇

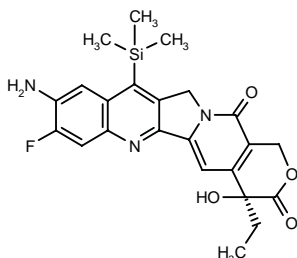
SOURCE – Glaxo Wellcome.

REFERENCES

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261493

9-Amino-4(*S*)-ethyl-8-fluoro-4-hydroxy-11-(trimethylsilyl)-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]-quinoline-3,14-dione



C23-H24-F-N3-O4-Si; Mol wt: 453.54

ACTION – Antineoplastic agent from a new class of lipophilic camptothecin derivatives, the 7-silylcamptothecins (silatecans), reported to be over 20 times more potent than camptothecin against HL-60, 833K and DC-3F cells *in vitro*.

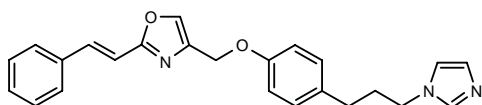
SOURCES – Univ. Kentucky, Lexington, KY (US); Univ. Pittsburgh, Pittsburgh, PA (US); Sloan-Kettering Cancer Cent., New York, NY (US).

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1. Chou, T.-C. et al. 7-Silylcamptothecins (silatecans): A new class of lipophilic camptothecins highly active against human cancers *in vitro* and *in vivo*. *Proc Amer Assoc Cancer Res* 1998, 39: Abst 1520.

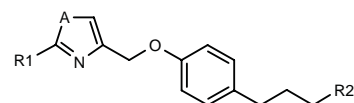
261544

4-[4-[3-(1-Imidazolyl)propyl]phenoxyethyl]-2-[2(*E*)-phenylvinyl]oxazole

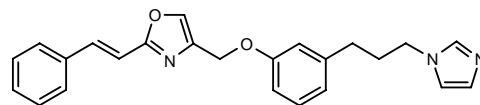


C24-H23-N3-O2; Mol wt: 385.46

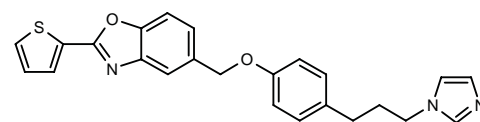
ACTION – Antineoplastic agent, an inhibitor of growth factor receptor tyrosine kinases, particularly HER2 (IC_{50} = 20 μ M), found to concentration-dependently inhibit HER2 phosphorylation in human breast cancer cells. Antiproliferative activity was demonstrated *in vitro* against human breast cancer MDA-MB-453 cells (IC_{50} = 0.25 μ M), as well as against other tumor cell lines such as pancreatic cancer APC-1 (IC_{50} = 2.5 μ M), colon cancer WiDr (IC_{50} = 2.1 μ M) and breast cancer T-47D (IC_{50} = 0.57 μ M), with no adverse effects on the proliferation of normal cells. *In vivo*, it dose-dependently (29-54% at 60-90 mg/kg/day p.o.) inhibited the growth of human breast cancer MDA-MB-453 implanted in athymic nude mice, and it also inhibited the growth of hormone-dependent prostate cancer LNCaP, especially in castrated animals. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	A	Formula
262130	(E)-CH=CHPh	1-imidazolyl-CH2	O	C ₂₅ H ₂₅ N ₃ O ₂
262132	4-(PhCH2O)-Ph	1-imidazolyl	O	C ₂₉ H ₂₇ N ₃ O ₃
262133	2-thienyl	1-imidazolyl	O	C ₂₀ H ₁₉ N ₃ O ₂ S
262134	5-Me-2-thienyl	1-imidazolyl	O	C ₂₁ H ₂₁ N ₃ O ₂ S
262135	5-Cl-2-thienyl	1-imidazolyl	O	C ₂₀ H ₁₈ ClN ₃ O ₂ S
262136	2-thienyl	1-imidazolyl	S	C ₂₀ H ₁₉ N ₃ OS ₂



262131: C24-H23-N3-O2



262137: C24-H21-N3-O2-S

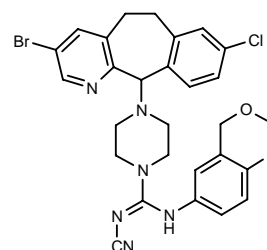
SOURCE – Takeda.

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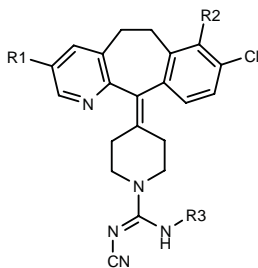
261579

*N*¹-(1,3-Benzodioxan-6-yl)-4-(3-bromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-*N*²-cyanopiperazin-1-carboxamide

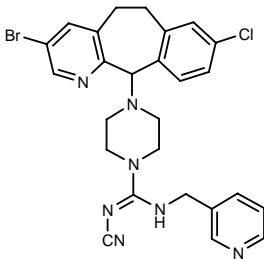


C28-H26-Br-Cl-N6-O2; Mol wt: 593.91

ACTION – Antineoplastic agent, a selective protein farnesyltransferase inhibitor (IC_{50} = 0.010 μ M), proven to block Ras processing in COS cells (IC_{50} < 0.25 μ M). Within this series of tricyclic *N*-cyanoimines, the following are also included:



Compound	R1	R2	R3	Formula
262586	H	H	1,3-benzodioxan-6-yl	C ₂₉ H ₂₆ ClN ₅ O ₂
262587	Br	H	1,3-benzodioxan-6-yl	C ₂₉ H ₂₅ BrClN ₅ O ₂
262588	Br	H	3-Pyr-CH ₂	C ₂₇ H ₂₄ BrClN ₆
262590	Br	H	4-Pip-CH ₂	C ₂₇ H ₃₀ BrClN ₆
262591	H	Br	1,3-benzodioxan-6-yl	C ₂₉ H ₂₅ BrClN ₅ O ₂
262592	Br	H	1-oxido-4-Pyr	C ₂₆ H ₂₂ BrClN ₆ O



262589: C₂₆-H₂₅-Br-Cl-N₇

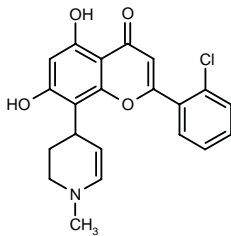
SOURCE – Schering Corp.

REFERENCES

1. Cooper, A.B. et al. (Schering Corp.) *Novel tricyclic N-cyanoimines useful as inhibitors of farnesyl-protein transferase*. WO 9804545.

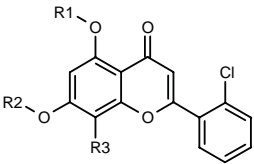
261903

2-(2-Chlorophenyl)-5,7-dihydroxy-8-(1-methyl-1,2,3,4-tetrahydropyridin-4-yl)-4*H*-1-benzopyran-4-one



C₂₁-H₁₈-Cl-N-O₄; Mol wt: 383.83

ACTION – Antineoplastic agent that acts by inhibiting cyclin-dependent kinases, particularly CDK/cyclin complexes such as CDK4/cyclin D1 (IC₅₀ < 50 μM). Compound was found to exhibit antiproliferative activity at concentrations as low as 0.2 μg/ml against breast cancer BT-549, MB-453 and MCF-7 cells, and at 1 μg/ml against bone cancer MG-63 cells. Within this series of chromone derivatives, the following are also included:



Compound	R1=R2	R3	Formula
261991	Me	1-Me-1,2,3,6-tetrahydro-4-Pyr	C ₂₃ H ₂₂ ClNO ₄
261992	Me	1-Me-3-oxo-4-Pip	C ₂₃ H ₂₂ ClNO ₅
261993	H	1-Me-3-oxo-4-Pip	C ₂₁ H ₁₈ ClNO ₅
261994	Me	cis-4-OH-1-Me-3-Pip	C ₂₃ H ₂₄ ClNO ₅
261995	H	cis-4-OH-1-Me-3-Pip	C ₂₁ H ₂₀ ClNO ₅

SOURCE – Mitotix.

REFERENCES

1. Mansuri, M.M. et al. (Mitotix, Inc.) *Inhibitors of cyclin dependent kinases*. US 5733920.

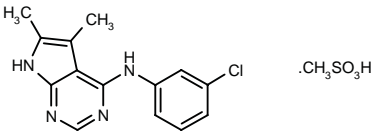
CGP-59326*

236874

229188 (as free base)

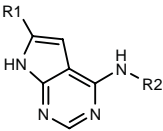
4-(3-Chlorophenylamino)-5,6-dimethyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine methanesulfonate

N-(3-Chlorophenyl)-*N*-(5,6-dimethyl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amine methanesulfonate

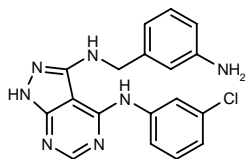


C₁₄-H₁₃-Cl-N₄.C-H₄-O₃-S; Mol wt: 68.84

ACTION – Antineoplastic agent with potent epidermal growth factor (EGF) receptor protein tyrosine kinase-inhibitory properties (IC₅₀ = 30 nM) and high selectivity versus nonreceptor tyrosine kinases and serine/threonine kinases. Compound inhibited the proliferation of a number of EGF receptor-expressing epithelial cell lines but exhibited no activity against EGF receptor-negative cell lines; it also inhibited the proliferation of human transitional cell carcinoma 253J B-V cells of the bladder. It displayed potent *in vivo* antitumor activity after oral administration, with an ED₅₀ of 1.56 mg/kg for inhibition of s.c. A-431 tumor growth in nude mice, and it also dose-dependently (1-40 mg/kg/day p.o.) inhibited the growth of 253J B-V tumors. In combination with cytotoxic agents, tumor regression and cures were obtained in animals bearing EGF receptor-positive human tumor xenografts. Other phenylamino-pyrrolo-pyrimidines include the following:



Compound	R1	R2	Formula
CGP-74321 [261823]	CONHMe	3-Cl-Ph	C ₁₄ H ₁₂ ClN ₅ O
CGP-75166 [261824]	4-OH-Ph	(R)-CH(Me)Ph	C ₂₀ H ₁₈ N ₄ O



CGP-76627 [261825]: C18-H16-Cl-N7

SOURCE – Novartis.

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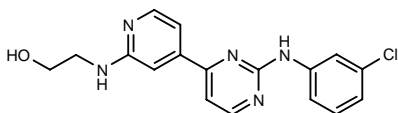
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*Identified compound **229188** Drug Data Rep 1996, 18(3): 278.

CGP-60474

260354

2-[4-[2-(3-Chlorophenylamino)pyrimidin-4-yl]pyridin-2-ylamino]ethanol



C17-H16-Cl-N5-O; Mol wt: 341.80

ACTION – Antineoplastic agent that potently and selectively inhibits the cyclin-dependent protein kinases cdk1 and cdk2 (IC_{50} = 20 and 50 nM, respectively). Compound displays potent antiproliferative activity *in vitro* (IC_{50} = 10-100 nM) against a variety of established human tumor cell lines, as well as potent antitumor activity *in vivo* against different human tumor xenografts (colon, small cell lung, non-small cell lung, breast, prostate, bladder) transplanted into nude mice when given both as a single agent and in combination with various cytotoxic agents (doxorubicin, vinblastine, cisplatin). CGP-60474 also appears to induce apoptosis in transformed cells.

SOURCE – Novartis.

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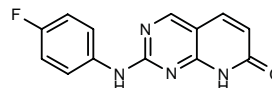
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PD-173956

261508

2-(4-Fluorophenylamino)pyrido[2,3-d]pyrimidin-7(8H)-one



C13-H9-F-N4-O; Mol wt: 256.24

ACTION – Potent and selective c-Src tyrosine kinase inhibitor (IC_{50} = 29 nM) that is at least 10-fold less potent toward platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF) receptor tyrosine kinases. In cell-based assays, title compound induced growth delay with IC_{50} values below 2.0 μ M.

SOURCE – Warner-Lambert.

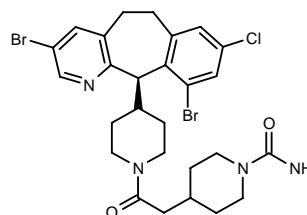
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SCH-66336*

254680

(+)-(R)-4-[2-[4-(3,10-Dibromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide



C27-H31-Br2-Cl-N4-O2; Mol wt: 638.83

ACTION – Orally active antineoplastic agent, a highly potent inhibitor of protein farnesyltransferase (IC_{50} = 1.9 nM) currently in phase I trials. The compound potently inhibited H-Ras processing in whole cells and blocked the growth of transformed fibroblasts and human tumor cell lines expressing activated K-Ras proteins, as well as human tumor cell lines lacking activated *ras* oncogenes. It also displayed potent oral activity against various human tumor xenografts in nude mice including colon, lung, pancreas, prostate and bladder tumors. Favorable pharmacokinetic properties were found in mice, rats and cynomolgus monkeys after oral administration, with an oral bioavailability of about 70 and 50%, respectively, in mice and monkeys, and studies in human tumor xenograft-bearing nude mice indicated that the drug readily reaches the tumor tissue after oral dosing.

SOURCE – Schering-Plough.

REFERENCES

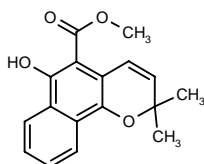
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- Liu, M. et al. *SCH 66336, an orally bioavailable tricyclic farnesyl protein transferase inhibitor, demonstrates broad and potent in-vivo antitumor activity*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1843.
- Njoroge, F.G. et al. *Orally active, trihalobenzocycloheptapyridine farnesyl protein transferase inhibitor antitumor agents*. Proc Amer Assoc Cancer Res 1998, 39: Abst 2176.
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*Identified compound **254680** (see **254082**) Drug Data Rep 1997, 19(10): 941.

ANTIANGIOGENIC AGENTS

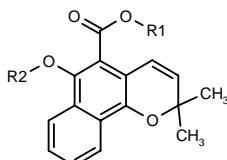
260514

6-Hydroxy-2,2-dimethyl-2H-naphtho[1,2-*b*]pyran-5-carboxylic acid methyl ester



C17-H16-O4; Mol wt: 284.31

ACTION – Cell adhesion inhibitor with potential as an antimetastatic agent and immunosuppressant. At 10 μ M compound produced 94 and 96% inhibition, respectively, of leukocyte and HL-60 cell adhesion to human vascular endothelial cells, without significantly affecting DNA synthesis. Within this series of naphtho[1,2-*b*]pyran derivatives, the following are also included:



Compound	R1	R2	Formula
261927	H	H	C ₁₈ H ₁₄ O ₄
261928	Me	Me	C ₁₈ H ₁₆ O ₄
261929	Et	H	C ₁₈ H ₁₆ O ₄

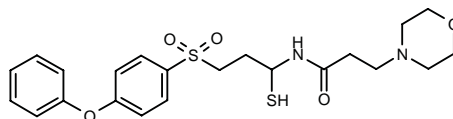
SOURCE – Kao.

REFERENCES

- Murase, T. et al. (Kao Corp.) *Cell adhesion inhibitors*. JP 98007556.

261515

3-(4-Morpholinyl)-N-[3-(4-phenoxyphenylsulfonyl)-1-sulfanylpropyl]propionamide



C22-H28-N2-O5-S2; Mol wt: 464.59

ACTION – Agent for the treatment of conditions associated with pathological matrix metalloproteinase (MMP) activity including tumor metastasis, invasion or angiogenesis, rheumatoid arthritis and corneal, epidermal or gastric ulceration. More particularly, the compound is a potent and selective inhibitor of collagenase III (MMP-13; IC₅₀ = 0.2 nM using recombinant human enzyme), with much weaker activity against collagenase I (MMP-1; IC₅₀ = 370 nM using recombinant human enzyme). In an *in vivo* angiogenesis assay, it inhibited the neovascularization of mouse corneal stroma by 51% at a dose of 50 mg/kg b.i.d. p.o.

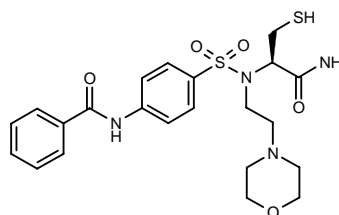
SOURCE – Monsanto.

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- Freskos, J.N. et al. (Monsanto Co.) *Thiol sulfone metalloprotease inhibitors*. WO 9803164.

261517

N-(4-Benzamidophenylsulfonyl)-N-[2-(4-morpholinyl)-ethyl]-L-cysteinamide



C22-H28-N4-O5-S2; Mol wt: 492.61

ACTION – An inhibitor of matrix metalloproteinases (MMP) with high potency and selectivity for collagenase III (MMP-13; IC₅₀ = 1.1 nM) and a negligible effect on collagenase I (fibroblast collagenase or MMP-1; IC₅₀ > 10,000 nM). Antiangiogenic activity was demonstrated *in vivo* in the corneal micropocket assay in mice, where it produced 37% inhibition of corneal stroma neo-vascularization at 50 mg/kg b.i.d. p.o. x 5 days. Potentially useful for the treatment of cancer and/or metastasis, as well as arthritis, corneal, epidermal or gastric ulceration, periodontal disease, Alzheimer's disease, thrombosis and bone disease.

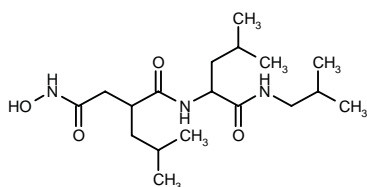
SOURCE – Monsanto.

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261873

2-[2-(*N*-Hydroxycarbamoylmethyl)-4-methylpentan-amido]-*N*-isobutyl-4-methylpentanamide



C18-H35-N3-O4; Mol wt: 357.49

ACTION – Antineoplastic agent, an inhibitor of gelatinase A (IC_{50} = 0.036 μ M) and gelatinase B (IC_{50} = 0.090 μ M), with activity against other matrix metalloproteinases (MMPs) such as collagenase (IC_{50} = 0.90 μ M), thermolysin (IC_{50} = 0.27 μ M) and stromelysin (IC_{50} = 0.17 μ M). Compound exhibited antitumor activity *in vivo* in mice bearing human HT-1080 tumors, producing 69.5% inhibition at 1 mg/day s.c. LD_{50} > 100 mg/kg s.c. in mice.

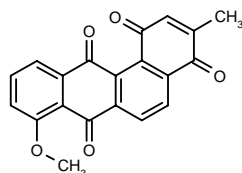
SOURCE – Banyu.

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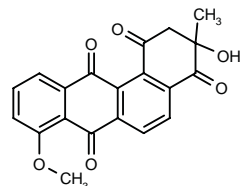
RUGATOCENONE A**262127**

8-Methoxy-3-methyl-1,4,7,12-tetrahydrobenz[a]-anthracene-1,4,7,12-tetraone



C20-H42-O5; Mol wt: 362.55

ACTION – Cell adhesion inhibitor isolated from *Actinomadura rugatobispora* TA-0291, proven to inhibit cell adhesion *in vitro* in human B lymphoma cells with an IC_{50} value of 3.95 μ g/ml. Another compound from this source is:



Rugatocenone B [262128]: C20-H14-O6

SOURCE – Taisho.

REFERENCES

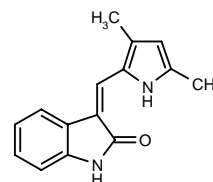
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SU-5416*

Product update

246676

(*Z*)-3-(3,5-Dimethylpyrrol-2-ylmethylene)indolin-2-one



C15-H14-N2-O; Mol wt: 238.29

ACTION – Antiangiogenic and antineoplastic agent, a potent inhibitor of Flk-1 receptor tyrosine kinase, as demonstrated against isolated enzyme (IC_{50} = 20 nM) and against murine VEGF (Flk-1)/KDR receptor tyrosine kinase expressed in mouse NIH3T3 cells (IC_{50} = 1.04 μ M), with 20-100-fold selectivity relative to human PDGF, EGF and IGF-1 receptor tyrosine kinases expressed in NIH3T3 cells (IC_{50} = 20.26, > 100 and > 100 μ M, respectively). It also displayed a potent (IC_{50} = 70 nM), selective (> 700-fold), fast-acting (5 min) and long-lasting (> 72 h) inhibitory effect on VEGF-stimulated human endothelial cell proliferation. *In vivo*, it exhibited high efficacy against s.c.-implanted A375 tumors in athymic mice at 25 mg/kg/day, inhibiting both neovascularization and tumor growth. It is currently undergoing phase I/II clinical studies in several solid tumors.

SOURCE – Sugen.

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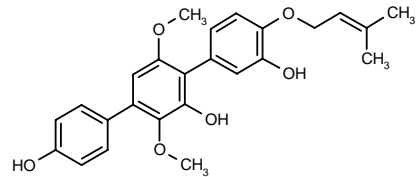
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4. Sun, L. et al. *Synthesis and biological evaluation of novel 3-(substituted pyrrol-2-yl)indolin-2-ones as potent and selective inhibitors of the FLK-1/KDR receptor tyrosine kinase*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 169.
5. Tang, C. et al. *SU5416: A potent and selective FLK-1/KDR kinase inhibitor that blocks receptor autophosphorylation, endothelial cell mitogenesis, and tumor growth*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 205.
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* Published with incorrect structure and chemical name, Drug Data Rep 1997, 19(4): 366.

MISCELLANEOUS
ANTINEOPLASTIC AGENTS

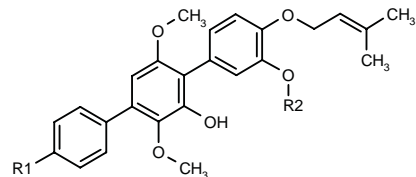
257713

3',6'-Dimethoxy-4-(3-methyl-2-butenyloxy)-*p*-terphenyl-2',3,4''-triol



C25-H26-O6; Mol wt: 422.48

ACTION – Immunosuppressive, antiinflammatory and antineoplastic agent isolated from a culture of *Aspergillus candidus* RF-5762 (FERM BP-5882). Compound inhibited the mitogenic response of concanavalin A- and lipopolysaccharide-stimulated murine spleen cells with IC₅₀ values of 1.2 and 4.5 ng/ml, respectively. Antitumor activity was demonstrated by inhibition of the proliferation of various tumor cells such as human non-small cell lung carcinoma Lu-99 cells (IC₅₀ = 1.0 ng/ml), murine leukemia P388 cells (IC₅₀ = 12.0 ng/ml) and human leukemia CCFR-CEM cells (IC₅₀ = 0.2 ng/ml), exerting no effect on normal human lung cells (IC₅₀ > 10,000 ng/ml). Other related compounds include the following:



Compound	R1	R2	Formula
262647	H	H	C ₂₅ H ₂₆ O ₅
262648	OH	Me	C ₂₆ H ₂₈ O ₆

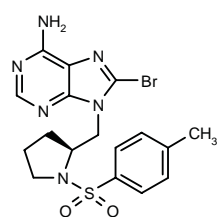
SOURCE – Shionogi.

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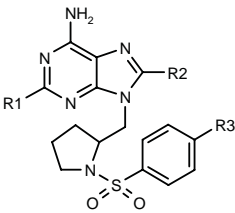
259197

8-Bromo-9-[1-(4-methylphenylsulfonyl)pyrrolidin-2(S)-ylmethyl]adenine



C17-H19-Br-N6-O2-S; Mol wt: 451.34

ACTION – Antineoplastic agent, with good antiproliferative activity against MT-4 cells (CC₅₀ = 0.10 µg/ml). Within this series of purine nucleoside derivatives, the following are also included:



Compound	R1	R2	R3	Isomer	Formula
262532	H	Br	Me	R	C ₁₇ H ₁₉ BrN ₆ O ₂ S
262533	H	Br	Me		C ₁₇ H ₁₉ BrN ₆ O ₂ S
262534	H	Br	i-Pr	S	C ₁₉ H ₂₃ BrN ₆ O ₂ S
262535	H	Br	i-Pr	R	C ₁₉ H ₂₃ BrN ₆ O ₂ S
262536	H	Br	i-Pr		C ₁₉ H ₂₃ BrN ₆ O ₂ S
262537	NH2	Br	Me	S	C ₁₇ H ₂₀ BrN ₇ O ₂ S
262538	NH2	Br	Me	R	C ₁₇ H ₂₀ BrN ₇ O ₂ S
262539	H	Et	Me	S	C ₁₉ H ₂₄ N ₆ O ₂ S
262540	H	i-Pr	Me	S	C ₂₀ H ₂₆ N ₆ O ₂ S

SOURCE – Nippon Paper.

REFERENCES

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260641

Poly-N-[(1-benzoyl-2-methyl-5-methoxy-3-indolyl)-acetyl]chitosan

ACTION – Agent for the treatment or prevention of colonic polyps without the side effects of nonsteroidal antiinflammatory drugs (NSAIDs), a representative compound from a series of esters and amides of pyrrole acetic acids.

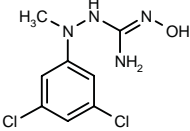
SOURCES – Univ. Arizona, Tucson, AR (US); Cell Pathways.

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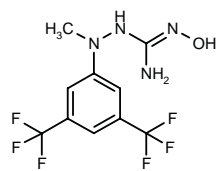
261505

1-[*N*-(3,5-Dichlorophenyl)-*N*-methylamino]-2-hydroxy-guanidine



C8-H10-Cl2-N4-O; Mol wt: 249.10

ACTION – Antineoplastic agent with the best *in vivo* antitumor profile from a series of *N*-hydroxy-*N'*-arylamino-guanidines, along with the following compound:



261506: C10-H10-F6-N4-O

The parent compound PKF-030-571 reportedly exerts selective growth-inhibitory effects against a panel of epithelial tumor cell lines compared to primary epithelial cells, and inhibits the growth of MDA-MB-435 and A-549 tumor xenografts at nontoxic doses.

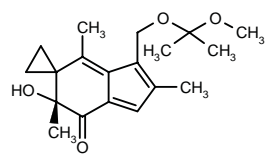
SOURCE – Novartis.

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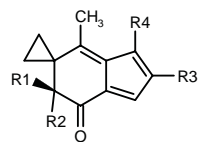
261529

6'-(*R*)-Hydroxy-3'-(1-methoxy-1-methylethoxymethyl)-2',4',6'-trimethyl-6',7'-dihydrospiro[cyclopropane-1,5'-[5'*H*]inden]-7'-one



C19-H26-O4; Mol wt: 318.41

ACTION – Antineoplastic agent with potent cytotoxicity when added to cultures of human lung carcinoma MV522 cells for 48 h (IC₅₀ = 930 ± 250 nM). It was also active *in vivo* in prolonging survival time in mice bearing MV522 tumors, with a significant effect when given at doses of 4, 8 or 16 mg/kg i.p. once daily for 5 consecutive days; it appeared to be more potent than the parent compound 6-hydroxymethyl acylfulvene (HMAF, also known as illudin S) and the maximum tolerated dose (MTD) was not reached. Other representative compounds within this series of illudin analogs include the following:



Compound	R1	R2	R3	R4	Formula
262368	Me	OH	Me	CH2OEt	C ₁₇ H ₂₂ O ₃
262369	Me	OH	Me	CH2SCH2CH(OH)CH2OH	C ₁₈ H ₂₄ O ₄ S
262370	-OCH2CH2O-	H		H	C ₁₄ H ₁₄ O ₃

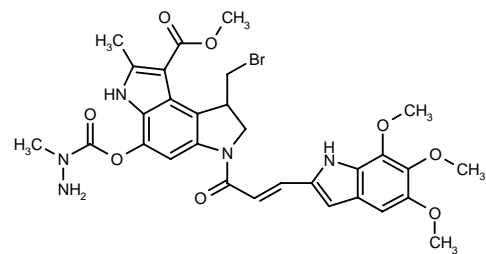
SOURCE – Univ. California, Oakland, CA (US).

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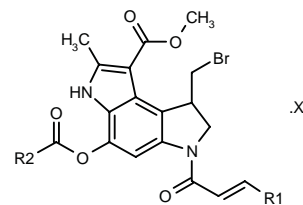
261546

5-(*N*-Amino-*N*-methylcarbamoyloxy)-1-(bromomethyl)-7-methyl-3-[3-(5,6,7-trimethoxy-1 *H*-indol-2-yl)-2 (*E*)-propenoyl]-1,2,3,7-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-8-carboxylic acid methyl ester

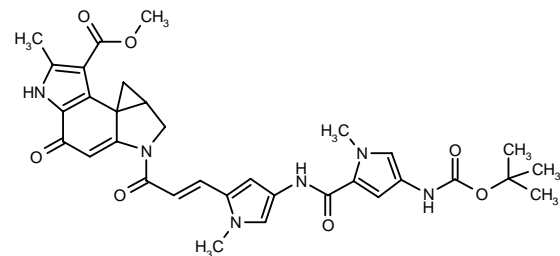


C30-H32-Br-N5-O8; Mol wt: 670.52

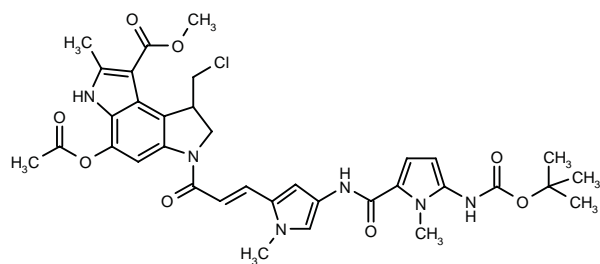
ACTION – Antineoplastic agent with potent cytotoxicity against HeLa S3 cells (IC₅₀ = 0.27 nM). *In vivo*, it inhibited the growth of sarcoma 180 tumors implanted s.c. in mice, with a T/C value of 0.07 at 2.0 mg/kg i.v. Other compounds from this series of DC-89 derivatives include the following:



Compound	R1	R2	X	Formula
262719	4-MeO-2-thienyl	Me		C ₂₄ H ₂₃ BrN ₂ O ₆ S
262720	4-MeO-2-thienyl	4-Me-1-Piz	HCl	C ₂₈ H ₃₁ BrN ₄ O ₆ S .HCl
262721	5,6,7-(MeO)3-2-indolyl	4-Me-1-Piz	HBr	C ₃₄ H ₃₈ BrN ₅ O ₈ .HBr
262722	5,6,7-(MeO)3-2-indolyl	Me		C ₃₀ H ₃₀ BrN ₃ O ₈
262723	4-NO2-1-Me-2-pyrrolyl	Me		C ₂₄ H ₂₃ BrN ₄ O ₇
262724	1-Me-4-(t-BuOCONH)-2-pyrrolyl	Me		C ₂₉ H ₃₃ BrN ₄ O ₇



262725: C33-H36-N6-O7



262726: C35-H39-Cl-N6-O8

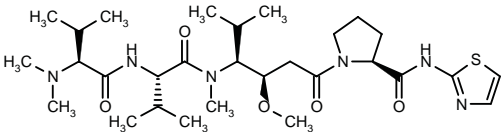
SOURCE – Kyowa Hakko.

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1. Amishiro, N. et al. (Kyowa Hakko Kogyo Co., Ltd.) *DC-89 derivs.* WO 9803509.

261561

N-[4(*S*)-[*N*-(*N,N*-Dimethyl-L-valyl-L-valyl)-*N*-methylamino]-3(*R*)-methoxy-5-methylhexanoyl]-L-proline 2-thiazolylamide



C29-H50-N6-O5-S; Mol wt: 594.81

ACTION – Antineoplastic agent, a dolastatin analog with improved therapeutic potential compared to dolastatin-10. It gave an IC₅₀ of 60 nM against colon carcinoma HT-29 cells and exhibited dose-dependent inhibition of tumor growth in mice bearing human breast tumors (MX-1) when given on days 5, 7, 9, 12, 14, 16, 19, 21 and 23 post-implantation at doses of 10, 20 and 30 mg/kg i.v.

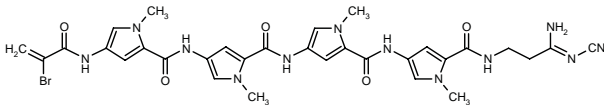
SOURCE – BASF.

REFERENCES

1. Barlozzri, T. et al. (BASF AG) *Tetrapeptide derivs. of dolastatin as antitumor agents.* WO 9804278.

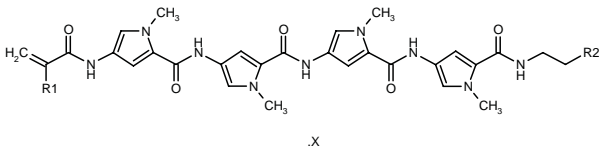
261569

3-[4-[4-[4-(2-Bromo-2-propenamido)-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-*N*-cyanopropionamide

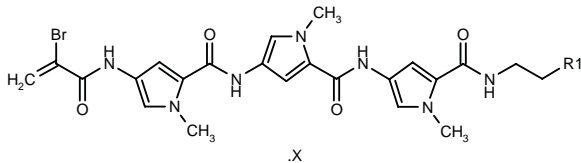


C31-H33-Br-N12-O5; Mol wt: 733.58

ACTION – Antineoplastic and antiviral agent reported to exert good *in vitro* and *in vivo* activity against murine leukemia L1210 and murine reticulosarcoma M5076. It also has activity against DNA and RNA viruses including herpesviruses, rhinoviruses and adenoviruses. Within this series of specifically claimed acryloyl substituted distamycin derivatives, the following are also included:



Compound	R1	R2	X	Formula
262509	Br	C(=NH)NHMe	HCl	C ₃₁ H ₃₈ BrN ₁₁ O ₅ .HCl
262510	Br	C(=NMe)NHMe	HCl	C ₃₂ H ₃₈ BrN ₁₁ O ₅ .HCl
262511	Br	C(=NOH)NH2		C ₃₀ H ₃₄ BrN ₁₁ O ₆
262512	Br	NHC(=NH)NH2	HCl	C ₃₀ H ₃₅ BrN ₁₂ O ₅ .HCl
262514	Br	CONH2		C ₃₀ H ₃₃ BrN ₁₀ O ₆
262516	Br	CN		C ₃₀ H ₃₁ BrN ₁₀ O ₅
262517	Cl	C(=NH)NHMe	HCl	C ₃₁ H ₃₆ ClN ₁₁ O ₅ .HCl



Compound	R1	X	Formula
262513	CN		C ₂₄ H ₂₅ BrN ₈ O ₄
262515	C(=NH)NHMe	HCl	C ₂₅ H ₃₀ BrN ₉ O ₄ .HCl

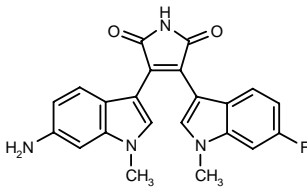
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Acryloyl subst. distamycin derivs., process for preparing them, and their use as antitumor and antiviral agents.* WO 9804524.

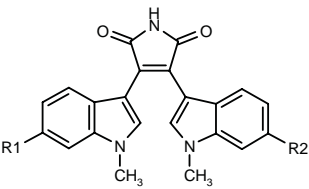
261582

3-(6-Amino-1-methylindol-3-yl)-4-(6-fluoro-1-methylindol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione



C22-H17-F-N4-O2; Mol wt: 388.40

ACTION – Antineoplastic agent reported to be particularly useful in the treatment or control of breast tumors; compound exhibited potent cytotoxicity against epithelial breast carcinoma MDA-MB-435 cells (IC₅₀ = 0.042 μM). Other specifically claimed compounds within this series of substituted bisindolylmaleimides include the following:



Compound	R1	R2	Formula
262574	NH2	CN	C ₂₃ H ₁₇ N ₅ O ₂
262575	OCH2Ph	NO2	C ₂₉ H ₂₂ N ₄ O ₅
262576	Cl	NO2	C ₂₂ H ₁₅ ClN ₄ O ₄
262577	OMe	OMe	C ₂₄ H ₂₁ N ₃ O ₄
262578	OMe	NHAc	C ₂₅ H ₂₂ N ₄ O ₄
262579	Me	CN	C ₂₄ H ₁₈ N ₄ O ₂

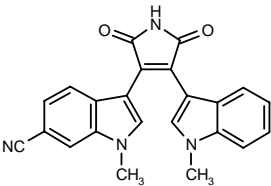
SOURCE – Roche.

REFERENCES

1. Dhingra, U.H. et al. (F. Hoffmann-La Roche AG) *Substd. bisindolylmaleimides for the inhibition of cell proliferation*. WO 9804551.

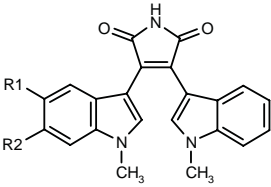
261583

1-Methyl-3-[4-(1-methylindol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl]indole-6-carbonitrile



C23-H16-N4-O2; Mol wt: 380.41

ACTION – Antiproliferative agent for the treatment of cancer, especially solid tumors, active *in vitro* against breast carcinoma MDA-MB-435 cells (IC₅₀ = 0.03 µM) and colon carcinoma SW480 cells (IC₅₀ = 0.008 µM). Other specifically claimed substituted bisindolylmaleimides include the following:



Compound	R1	R2	Formula
262605	CN	H	C ₂₃ H ₁₆ N ₄ O ₂
262606	H	CH2CO2Me	C ₂₆ H ₂₁ N ₃ O ₄
262607	H	CHO	C ₂₃ H ₁₇ N ₃ O ₃
262608	H	CH2OMe	C ₂₄ H ₂₁ N ₃ O ₃
262609	H	CH2OH	C ₂₃ H ₁₉ N ₃ O ₃
262610	H	CONH2	C ₂₃ H ₁₈ N ₄ O ₃

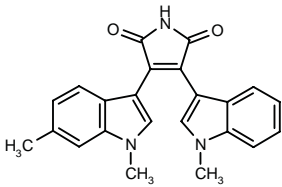
SOURCE – Roche.

REFERENCES

1. Huryn, D.M. and Keith, D.D. (F. Hoffmann-La Roche AG) *Substd. bisindolylmaleimides for the inhibition of cell proliferation*. WO 9804552.

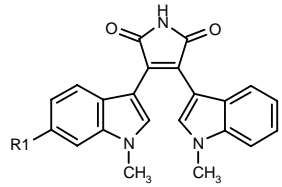
261584

3-(1,6-Dimethylindol-3-yl)-4-(1-methylindol-3-yl)-2,5-dihydro-1H-pyrrole-2,5-dione



C23-H19-N3-O2; Mol wt: 369.42

ACTION – Antiproliferative agent active *in vitro* against breast carcinoma MDA-MB-435 cells (IC₅₀ = 0.033 µM) and colon carcinoma SW480 cells (IC₅₀ = 0.029 µM). Particularly useful for the treatment of solid tumors. Other specifically claimed substituted bisindolylmaleimides include the following:



Compound	R1	Formula
262611	SMe	C ₂₃ H ₁₉ N ₃ O ₂ S
262612	OH	C ₂₂ H ₁₇ N ₃ O ₃
262613	Et	C ₂₄ H ₂₁ N ₃ O ₂
262614	CH2CN	C ₂₄ H ₁₈ N ₄ O ₂

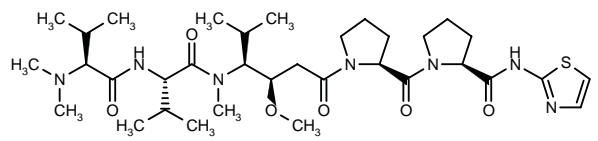
SOURCE – Roche.

REFERENCES

1. Dhingra, U.H. et al. (F. Hoffmann-La Roche AG) *Substd. bisindolylmaleimides for the inhibition of cell proliferation*. WO 9804553.

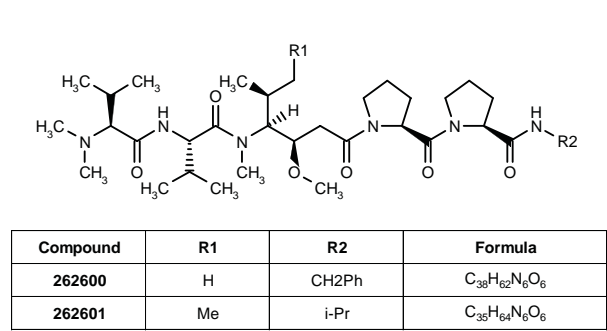
261591

N-[4(S)-[N(N,N-Dimethyl-L-valyl-L-valyl)-N-methylamino]-3(R)-methoxy-5-methylhexanoyl]-L-prolyl-L-proline 2-thiazolylamide



C34-H57-N7-O6-S; Mol wt: 691.93

ACTION – Antineoplastic agent, a derivative of dolastatin 10 reported to possess improved activity compared to the parent compound. *In vitro*, it exhibited potent cytotoxicity against colon carcinoma HT-29 cells, with an IC₅₀ value of 2 nM. Other compounds from this series of dolastatin pentapeptides include the following:



SOURCE – BASF.

REFERENCES

1. Barlozzri, T. et al. (BASF AG) *Dolastatin pentapeptide derivs. and their use as antitumor agents*. WO 9804581.

261639

Telomerase antisense oligonucleotide whose sequence is: 5'-TAGGGTTAGACAA-3'

ACTION – Telomerase antisense oligonucleotide with potent growth-inhibitory activity against human lung cancer A427, A549 and RERF-LC-AI cells in liposomes (50-60% inhibition at 1 μM for 24 h), but not without liposomes; it also significantly enhanced the growth-inhibitory activity of subtherapeutic concentrations of anticancer agents (cisplatin, etoposide, mitomycin C). The antisense compound with liposomes markedly reduced telomerase activity in these cells.

SOURCES – Kureha; Taisho.

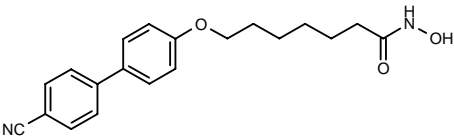
REFERENCES

1. Kato, H. et al. *In vitro tumor growth inhibition by telomerase antisense and anticancer agents*. Proc Amer Assoc Cancer Res 1998, 39: Abst 2833.

A-161906*

252369

7-(4'-Cyanobiphenyl-4-yloxy)heptanohydroxamic acid



C20-H22-N2-O3; Mol wt: 338.41

ACTION – Small-molecule transforming growth factor-β (TGF-β) mimetic with pure TGF-β-like agonist activity in mink lung epithelial Mv1Lu cells stably transfected with a TGF-β-responsive PAI-1 promoter/luciferase construct. It also inhibited CCL-64, mouse keratinocyte, HTC-116 and human dermal fibroblast cell proliferation in a concentration-dependent manner by arresting cell growth in G1/S. A-161906 increased fibronectin production and inhibited IL-1-induced collagenase expression in fibroblasts and IL-8 expression in A549 cells. Its site of action appears to be distal to TGF-β receptors and it may affect signaling events controlled by Smad4. It was previously reported to inhibit matrix metalloproteinases and tumor necrosis factor (TNF-α) release.

SOURCE – Abbott.

REFERENCES

1. Fesik, S.W. et al. (Abbott Labs.) *Biphenyl hydroxamate inhibitors of matrix metalloproteinases*. US 5665777, WO 9718188.
2. Glaser, K.B. et al. *Biaryl hydroxymates: Small molecule TGFβ mimetics*. Proc Amer Assoc Cancer Res 1998, 39: Abst 1198.

*Identified compound 252369 Annu Drug Data Rep 1997, 19(9): 830.

FMH-1

261174

ACTION – Human interleukin-1β-converting enzyme (ICE)/CED-3-like protease with the ability to induce apoptosis. Polynucleotides encoding the novel protein are provided for use in gene therapy for inducing apoptosis in disorders such as cancer, autoimmune diseases and persistent infections.

SOURCE – Genetics Inst.

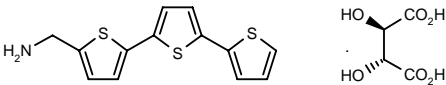
REFERENCES

1. Bowman, M.R. (Genetics Inst., Inc.) *Protease FMH-1, an ICE/CED-like protease*. WO 9800554.

NSC-660641

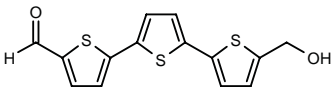
262749

5-(Aminomethyl)-2,2':5',2''-terthiophene L-tartrate



C13-H11-N-S3.C4-H6-O6; Mol wt: 427.50

ACTION – Antineoplastic agent proven to inhibit tumor growth in mice with s.c. implanted ras-transformed human bronchial epithelial cells (76% inhibition of tumor growth at 12 mg/kg/day i.p. at week 7 after tumor implantation). Another compound from this series of polythiophenes is:



NSC-647455 [262782]: C14-H10-O2-S3

SOURCES – Ind. Technol. Res. Inst., Hsinchu (TW); Purdue Res. Found., W. Lafayette, IN (US).

REFERENCES

1. Chang, C.T. et al. (Purdue Res. Found.; Ind. Technol. Res. Inst. [TW]) *Polythiophene anti-tumor agents*. US 5741811.

PEG-rMETase

260907

Polyethylene glycol (PEG)-conjugated recombinant methioninase (rMETase) with a molecular mass of approximately 53 kD indicating the conjugation of 2 PEG molecules per subunit of rMETase and 8 per tetramer

ACTION – Antineoplastic agent, a recombinant methioninase* (rMETase)–polyethylene glycol conjugate with increased serum half-life in rats compared to unmodified rMETase (160 min vs. 80 min), and a longer duration of action, as demonstrated by depletion of serum methionine levels to < 0.1 μ M for about 8 h compared to 2 h for rMETase in rats. Antitumor activity was shown *in vitro* against human lung and kidney cancer cells, with IC₅₀ values of 0.04 and 0.06 U/ml, respectively; tumor selectivity was demonstrated by much higher IC₅₀ values for normal lung and kidney cells (IC₅₀ = 0.8 and 1.5 U/ml, respectively).

SOURCE – AntiCancer.

REFERENCES

1. Tan, Y. et al. *Polyethylene glycol conjugation of recombinant methioninase for cancer therapy*. 8th Int Cong Anti-Cancer Treat (Feb 3-6, Paris) 1998, Abst O58.
2. Tan, Y. et al. *Polyethylene glycol conjugation of recombinant methioninase for cancer therapy*. *Protein Expr Purif* 1998, 12(1): 45.

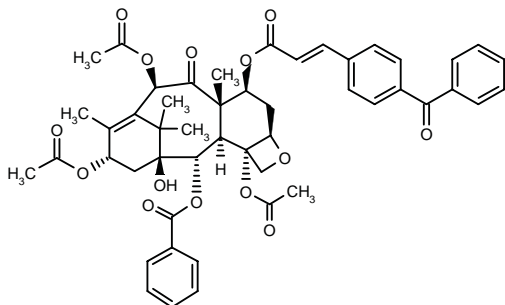
*See **AC-9301** Drug Data Rep 1995, 17(6): 573.

RESISTANCE MODIFIERS

SB-RA-31012

261723

[2a*R*-(2a α ,4 β ,4a β ,6 β ,9 α ,11 β ,12 α ,12a α ,12b α)]-6,9,12b-Triacetox-12-benzoyloxy-4-[3-(4-benzoylphenyl)-2(*E*)-propenoyloxy]-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C49-H50-O14; Mol wt: 862.93

ACTION – Multidrug resistance (MDR)-reversing agent shown to block the P-glycoprotein efflux system, allowing antineoplastic drugs to penetrate into and accumulate in MDR tumor cells. Its activity was demonstrated against drug-resistant human breast cancer cells when co-administered with paclitaxel (92-94% MDR reversal at 0.1 μ M) or doxorubicin (96% MDR reversal at 1 μ M).

Compound was not cytotoxic even at 30 μ M, indicating an excellent therapeutic index. A lead compound from a series of noncytotoxic, hydrophobic taxane derivatives.

SOURCES – Roswell Park Cancer Inst., Buffalo, NY (US); State Univ. New York at Stony Brook, Stony Brook, NY (US).

REFERENCES

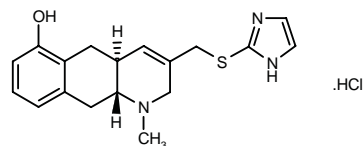
1. Ojima, I. et al. *Structure-activity relationship studies of new taxanes as reversal agents for multi-drug resistance in cancer cells*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 012.

OCULAR MEDICATIONS

ANTIGLAUCOMA AGENTS

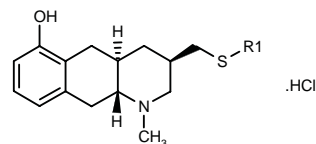
261205

(4a*S*,10a*R*)-3-(2-Imidazolylsulfanylmethyl)-1-methyl-1,2,4a,5,10,10a-hexahydrobenzo[*g*]quinolin-6-ol hydrochloride

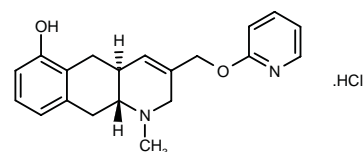


C18-H21-N3-O-S.HCl; Mol wt: 363.90

ACTION – Agent for the treatment of glaucoma proven to decrease intraocular pressure in rabbits by 3.3 mmHg at a dose of 0.9 μ mol as eye drops and to increase blood flow in the optic nerve of rats by 30% after a dose of 0.1 mg/kg s.c. It is also reported to be useful for the treatment of myopia by virtue of its dopaminomimetic activity, as shown by its ability to inhibit electrically evoked acetylcholine release from striatal slices at concentrations of 1-100 nM. Other specifically claimed compounds from this series of benzo[*g*]quinolines include the following:



Compound	R1	Formula
261706	4-Me-4H-1,2,4-triazol-3-yl	C ₁₈ H ₂₄ N ₄ OS.HCl
261708	1-oxido-2-Pyr	C ₂₀ H ₂₄ N ₂ O ₂ S.HCl



261707: C20-H22-N2-O2.HCl

PEG-rMETase

260907

Polyethylene glycol (PEG)-conjugated recombinant methioninase (rMETase) with a molecular mass of approximately 53 kD indicating the conjugation of 2 PEG molecules per subunit of rMETase and 8 per tetramer

ACTION – Antineoplastic agent, a recombinant methioninase* (rMETase)–polyethylene glycol conjugate with increased serum half-life in rats compared to unmodified rMETase (160 min vs. 80 min), and a longer duration of action, as demonstrated by depletion of serum methionine levels to < 0.1 μM for about 8 h compared to 2 h for rMETase in rats. Antitumor activity was shown *in vitro* against human lung and kidney cancer cells, with IC₅₀ values of 0.04 and 0.06 U/ml, respectively; tumor selectivity was demonstrated by much higher IC₅₀ values for normal lung and kidney cells (IC₅₀ = 0.8 and 1.5 U/ml, respectively).

SOURCE – AntiCancer.

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1. Tan, Y. et al. *Polyethylene glycol conjugation of recombinant methioninase for cancer therapy*. 8th Int Cong Anti-Cancer Treat (Feb 3-6, Paris) 1998, Abst O58.
2. Tan, Y. et al. *Polyethylene glycol conjugation of recombinant methioninase for cancer therapy*. *Protein Expr Purif* 1998, 12(1): 45.

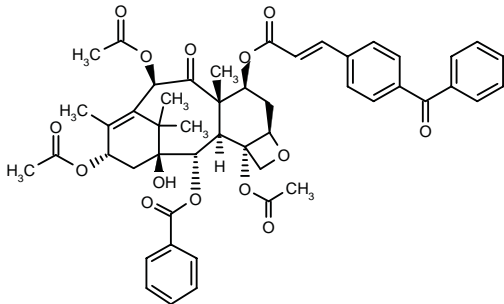
*See **AC-9301** Drug Data Rep 1995, 17(6): 573.

RESISTANCE MODIFIERS

SB-RA-31012

261723

[2a*R*-(2α,4β,4aβ,6β,9α,11β,12α,12aα,12bα)]-6,9,12b-Triacetox-12-benzoyloxy-4-[3-(4-benzoylphenyl)-2(*E*)-propenoyloxy]-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C49-H50-O14; Mol wt: 862.93

ACTION – Multidrug resistance (MDR)-reversing agent shown to block the P-glycoprotein efflux system, allowing antineoplastic drugs to penetrate into and accumulate in MDR tumor cells. Its activity was demonstrated against drug-resistant human breast cancer cells when co-administered with paclitaxel (92-94% MDR reversal at 0.1 μM) or doxorubicin (96% MDR reversal at 1 μM).

Compound was not cytotoxic even at 30 μM, indicating an excellent therapeutic index. A lead compound from a series of noncytotoxic, hydrophobic taxane derivatives.

SOURCES – Roswell Park Cancer Inst., Buffalo, NY (US); State Univ. New York at Stony Brook, Stony Brook, NY (US).

REFERENCES

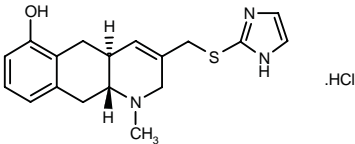
1. Ojima, I. et al. *Structure-activity relationship studies of new taxanes as reversal agents for multi-drug resistance in cancer cells*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 012.

OCULAR MEDICATIONS

ANTI GLAUCOMA AGENTS

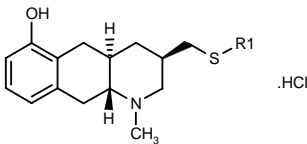
261205

(4a*S*,10a*R*)-3-(2-Imidazolylsulfanylmethyl)-1-methyl-1,2,4a,5,10,10a-hexahydrobenzo[*g*]quinolin-6-ol hydrochloride

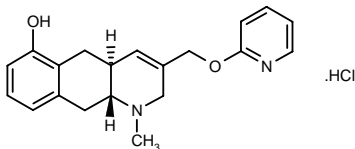


C18-H21-N3-O-S.HCl; Mol wt: 363.90

ACTION – Agent for the treatment of glaucoma proven to decrease intraocular pressure in rabbits by 3.3 mmHg at a dose of 0.9 μmol as eye drops and to increase blood flow in the optic nerve of rats by 30% after a dose of 0.1 mg/kg s.c. It is also reported to be useful for the treatment of myopia by virtue of its dopaminomimetic activity, as shown by its ability to inhibit electrically evoked acetylcholine release from striatal slices at concentrations of 1-100 nM. Other specifically claimed compounds from this series of benzo[*g*]quinolines include the following:



Compound	R1	Formula
261706	4-Me-4H-1,2,4-triazol-3-yl	C ₁₈ H ₂₄ N ₄ OS.HCl
261708	1-oxido-2-Pyr	C ₂₀ H ₂₄ N ₂ O ₂ S.HCl



261707: C20-H22-N2-O2.HCl

SOURCE – Novartis.

REFERENCES

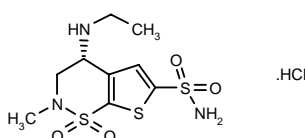
1. Gull, P. et al. (Novartis AG) *Benzo[g]quinoline derivs.* WO 9801444.

AL-4414A*

261465

177539 (as free base)

(+)-(R)-4-(Ethylamino)-2-methyl-3,4-dihydro-2H-thieno-[3,2-e][1,2]thiazine-6-sulfonamide 1,1-dioxide hydrochloride



C9-H15-N3-O4-S3.HCl; Mol wt: 361.88

ACTION – Agent representative of a new class of topically active, water-soluble carbonic anhydrase inhibitors, identified as a clinical candidate for the treatment of glaucoma and ocular hypertension.

SOURCE – Alcon.

REFERENCES

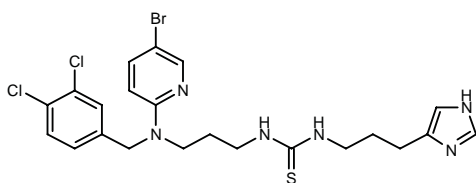
1. Dean, T.R. et al. (Alcon Labs., Inc.) *Thiophene sulfonamides useful as carbonic anhydrase inhibitors.* EP 527801, JP 93508832, US 5153192, US 5240923, WO 9115486.
2. Dean, T.R. et al. (Alcon Labs., Inc.) *Sulfonamides useful as carbonic anhydrase inhibitors.* US 5378703.
3. Dean, T.R. and Desantis, L. Jr. (Alcon Labs., Inc.) *Topical antiglaucoma compns. comprising carbonic anhydrase inhibitors and beta-blockers.* EP 625903, WO 9316701.
4. Lang, J.C. et al. (Alcon Labs., Inc.) *Use of carrageenans in topical ophthalmic compns.* EP 495421, US 5403841.
5. DuPriest, M.T. et al. *Enantioselective synthesis of AL-4414A, a topically active carbonic anhydrase inhibitor.* J Org Chem 1997, 62(26): 9372.

*Identified compound **177539** Drug Data Rep 1992, 14(4): 305.

NNC-26-9100*

259487

N-[3-[N-(5-Bromo-2-pyridyl)-N-(3,4-dichlorobenzyl)-amino]propyl]-N'-[3-(1H-imidazol-4-yl)propyl]thiourea



C22-H25-Br-Cl2-N6-S; Mol wt: 556.35

ACTION – Nonpeptide somatostatin receptor full agonist with high affinity for the sst4 subtype ($K_i = 6$ nM for inhibition of [125 I]-[Tyr¹]-SRIF binding to membranes from transfected mammalian cells) and more than 100-fold selectivity over the other four subtypes (sst1, sst2, sst3

and sst5) and a variety of other G-protein-coupled receptors. In a functional assay, the compound almost completely inhibited (95% efficacy) the forskolin-induced accumulation of cAMP in BHK cells expressing the human sst4 receptor, with an EC_{50} of 2 nM. Potentially useful for the treatment of various diseases related to somatostatin receptor malfunction such as glaucoma.

SOURCE – Novo Nordisk.

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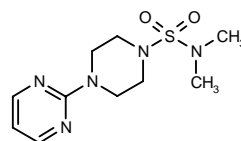
1. Ankersen, M. et al. (Novo Nordisk A/S) *Somatostatin agonists and antagonists.* WO 9743278.
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*Identified compound **259487** (see **258992**) Drug Data Rep 1998, 20(3): 238.

ANTICATARACT AGENTS

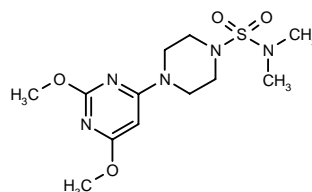
258436

N,N-Dimethyl-4-(2-pyrimidinyl)piperazine-1-sulfonamide



C10-H7-N5-O2-S; Mol wt: 261.26

ACTION – Anticataract agent shown to prevent cataract development in streptozotocin-treated rats following administration in the diet. Another related compound is:



262652: C12-H21-N5-O4-S

SOURCE – Senju.

REFERENCES

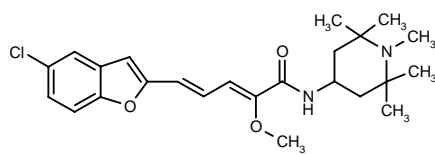
1. Inoue, J. et al. (Senju Pharm. Co., Ltd.) *Anti-cataract agents.* EP 806422, JP 97301868.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

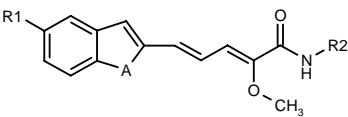
261203

(2*Z*,4*E*)-5-(5-Chlorobenzofuran-2-yl)-2-methoxy-*N*-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,4-pentadienamide



C24-H31-Cl-N2-O3; Mol wt: 430.97

ACTION – Agent for the treatment of osteoporosis, Paget’s disease, hyperparathyroidism and related diseases that acts by inhibiting bone resorption through selective inhibition of mammalian osteoclast vacuolar ATPase. Compound was found to inhibit bafilomycin-sensitive ATPase in chicken osteoclasts with an IC₅₀ value of 0.5 μM. Also expected to possess antitumor, antiviral, antiulcer, immunosuppressant, hypolipidemic, antiatherosclerotic and antiangiogenic activity. Other compounds from this series of heteroaryl pentadienoic acid derivatives include the following:



Compound	R1	R2	A	Formula
261709	H	1,2,2,6,6-(Me)5-4-Pip	O	C ₂₃ H ₃₀ N ₂ O ₃
261710	H	1,2,2,6,6-(Me)5-4-Pip	O	C ₂₄ H ₃₂ N ₂ O ₃
261711	Cl	(CH ₂) ₃ N(Et) ₂	O	C ₂₁ H ₂₇ ClN ₂ O ₃
261712	H	1,2,2,6,6-(Me)5-4-Pip	S	C ₂₄ H ₃₂ N ₂ O ₂ S

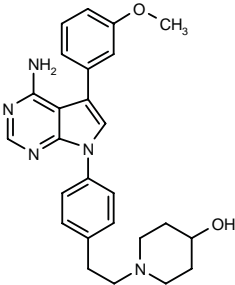
SOURCE – SmithKline Beecham.

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1. Farina, C. et al. (SmithKline Beecham SpA; SmithKline Beecham Labs. Pharm.) *Heteroaromatic pentadienoic acid derivs. useful as inhibitors of bone resorption*. WO 9801436.

262048

7-[4-[2-(4-Hydroxypiperidin-1-yl)ethyl]phenyl]-5-(3-methoxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



C26-H29-N5-O2; Mol wt: 443.55

ACTION – Bone resorption inhibitor that acts by inhibiting the activity of protein tyrosine kinase pp60^{c-Src} (IC₅₀ = 20 nM), with specificity over other kinases. Compound displayed potent antiresorptive activity in an *in vivo* model of hypercalcemia induced by IL-1β in mice at s.c. doses of 1-25 mg/kg b.i.d. Potentially useful for the treatment of diseases characterized by excessive bone resorption such as osteoporosis and tumor-induced hypercalcemia, as well as c-Src-overexpressing tumors such as colon carcinoma.

SOURCE – Novartis.

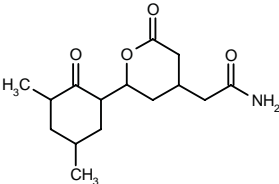
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A-75943

259194

2-[2-(3,5-Dimethyl-2-oxocyclohexyl)-6-oxotetrahydropyran-4-yl]acetamide



C15-H23-N-O4; Mol wt: 281.35

ACTION – Bone resorption inhibitor for the treatment of osteoporosis and hypercalcemia isolated from *Streptomyces* sp. SANK 61296 (FERM BP-5505).

SOURCE – Sankyo.

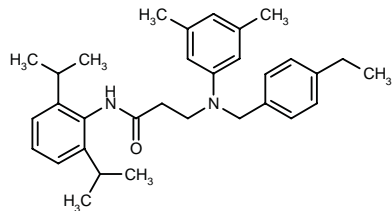
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TREATMENT OF LIPOPROTEIN DISORDERS

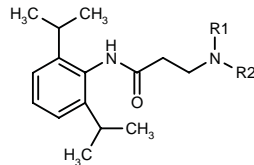
261213

N-(2,6-Diisopropylphenyl)-3-[N-(3,5-dimethylphenyl)-N-(4-ethylphenyl)amino]propionamide



C32-H42-N2-O; Mol wt: 470.70

ACTION – Hypolipidemic and antiatherosclerotic agent with ACAT-inhibitory activity, as demonstrated in THP-1 and HepG2 cells (IC₅₀ = 4.6 and 2.7 nM, respectively). *In vivo*, it produced a 50.4% decrease in total cholesterol in Golden hamsters at 50 mg/kg/day p.o. x 5 days. A representative compound from a series of propionanilide derivatives, wherein the following are also included:



Compound	R1	R2	Formula
262278	C6H13	3,5-(Me)2-Ph	C ₂₉ H ₄₄ N ₂ O
262279	Ph	4-Ph-1-Piz-CH2CH2	C ₃₃ H ₄₄ N ₄ O
262280	C6H13	Ph	C ₂₇ H ₄₀ N ₂ O
262281	1,3-benzo-dioxol-5-yl-CH2	3,5-(Me)2-Ph	C ₃₁ H ₃₈ N ₂ O ₃
262282	4,6-(Me)2-2-Pyr	1,3-benzodioxol-5-yl-SO2	C ₂₉ H ₃₀ N ₃ O ₅ S
262283	3,5-(Me)2-Ph	1,3-benzodioxol-5-yl-SO2	C ₃₀ H ₃₆ N ₂ O ₅ S

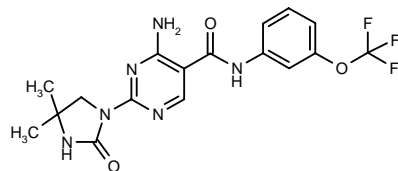
SOURCE – Yamanouchi.

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260850

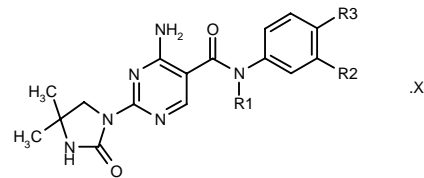
4-Amino-2-(4,4-dimethyl-2-oxoimidazolidin-1-yl)-N-[3-(trifluoromethoxy)phenyl]pyrimidine-5-carboxamide



C17-H17-F3-N6-O3; Mol wt: 410.35

ACTION – Hypolipidemic agent proven to stimulate the expression of LD receptor mRNA in rat liver (250% [controls = 100%] after administration of 30 mg/kg) while

being devoid of the cytotoxic effects of structurally related compounds. Other compounds from this series of 4-amino-2-ureidopyrimidine-5-carboxamides include the following:



Compound	R1	R2	R3	.X	Formula
261917	Et	OCF3	H	HCl	C ₁₉ H ₂₁ F ₃ N ₆ O ₃ .HCl
261918	CH2CF3	OCF3	H		C ₁₉ H ₁₈ F ₆ N ₆ O ₃
261919	H	-OCF2O-		HCl	C ₁₇ H ₁₆ F ₂ N ₆ O ₄ .HCl
261920	H	-OCF2CF2O-		HCl	C ₁₈ H ₁₆ F ₄ N ₆ O ₄ .HCl
261921	H	SCF3	H	HCl	C ₁₇ H ₁₇ F ₃ N ₆ O ₂ S.HCl

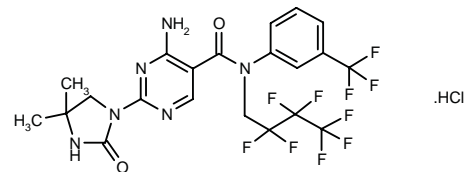
SOURCE – Hoechst Marion Roussel.

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1. Böger, H.G. et al. (Hoechst AG) *4-Amino-2-ureido-pyrimidine-5-carboxamides, processes for their preparation, medicaments containing these cpds., and their use*. EP 816358, JP 98072463.

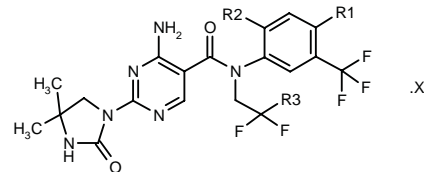
260851

4-Amino-2-(4,4-dimethyl-2-oxoimidazolidin-1-yl)-N-(2,2,3,3,4,4,4-heptafluorobutyl)-N-[3-(trifluoromethyl)phenyl]pyrimidine-5-carboxamide hydrochloride



C21-H18-F10-N6-O2.HCl; Mol wt: 612.86

ACTION – Hypolipidemic agent proven to stimulate the expression of LDL receptor mRNA in rat liver (245% [controls = 100%] after administration of 30 mg/kg) and which possesses greatly improved metabolic stability compared with known structurally related compounds. Other compounds from this series of 4-amino-2-ureidopyrimidin-5-carboxamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
261804	H	H	F	HCl	C ₁₉ H ₁₈ F ₈ N ₆ O ₂ .HCl
261805	H	H	CF3	HCl	C ₂₀ H ₁₈ F ₈ N ₆ O ₂ .HCl
261806	F	H	F		C ₁₉ H ₁₇ F ₇ N ₆ O ₂
261807	Cl	H	F	HCl	C ₁₉ H ₁₇ ClF ₈ N ₆ O ₂ .HCl
261808	Cl	H	CF3		C ₂₀ H ₁₇ ClF ₈ N ₆ O ₂
261809	Cl	H	CF2CF3		C ₂₁ H ₁₇ ClF ₁₀ N ₆ O ₂
261810	H	Cl	CF3	HCl	C ₂₀ H ₁₇ ClF ₈ N ₆ O ₂ .HCl
261811	H	Cl	CF2CF3		C ₂₁ H ₁₇ ClF ₁₀ N ₆ O ₂
261812	F	H	CF2CF3		C ₂₁ H ₁₇ F ₁₁ N ₆ O ₂

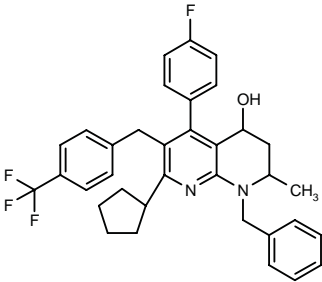
SOURCE – Hoechst Marion Roussel.

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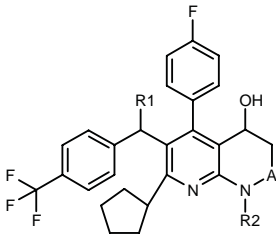
260857

1-Benzyl-7-cyclopentyl-5-(4-fluorophenyl)-2-methyl-6-[4-(trifluoromethyl)benzyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-4-ol



C35-H34-F4-N2-O; Mol wt: 574.66

ACTION – Hypolipidemic and antiatherosclerotic agent that acts by inhibiting cholesteryl ester transfer protein (CETP). Compound inhibited CETP in an *ex vivo* assay in hamsters, giving 50.4% inhibition at 10 mg/kg i.v. *In vivo*, it produced a 9.21% increase in HDL cholesterol levels when administered orally at 2 mg/kg x 3 to hamsters. When tested in transgenic hCETP mice at 80 ppm in the diet, it produced a 14.5% increase in serum HDL levels, while reducing serum triglycerides by 24.5%. Other compounds from this series of heterocyclic condensed pyridine derivatives include the following:



Compound	R1	R2	A	Formula
261791	F	H	S	C ₂₆ H ₂₃ F ₅ N ₂ OS
261792	OH	H	SO ₂	C ₂₆ H ₂₄ F ₄ N ₂ O ₄ S
261793	H	CH ₂ Ph	CH ₂	C ₃₄ H ₃₂ F ₄ N ₂ O
261794	OH	CH ₂ Ph	CH(Me)	C ₃₅ H ₃₄ F ₄ N ₂ O ₂

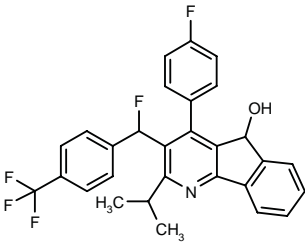
SOURCE – Bayer.

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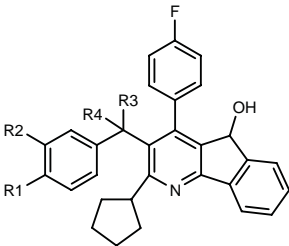
262090

4-(4-Fluorophenyl)-3-[1-fluoro-1-[4-(trifluoromethyl)phenyl]methyl]-2-isopropyl-5H-indeno[1,2-b]pyridin-5-ol

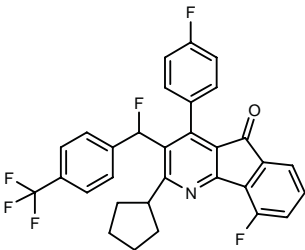


C29-H22-F5-N-O; Mol wt: 495.49

ACTION – Hypolipidemic and antiatherosclerotic agent that acts by inhibiting cholesteryl ester transfer protein (CETP), as shown *in vitro* (IC₅₀ = 60 nM) and *ex vivo* in Golden hamsters (64.0% inhibition at 10 mg/kg i.v.). *In vivo*, it increased HDL cholesterol (22.0%) and reduced LDL cholesterol (10.5%) and triglycerides (9.7%) when given in the diet at 100 ppm to transgenic hCETP mice. Other compounds from this series of fused pyridines include the following:



Compound	R1	R2	R3	R4	Formula
262958	CF3	H	F	H	C ₃₁ H ₂₄ F ₅ NO
262959	CF3	H	-O-		C ₃₁ H ₂₃ F ₄ NO ₂
262960	CF3	H	H	H	C ₃₁ H ₂₅ F ₄ NO
262961	Cl	CF3	OH	H	C ₃₁ H ₂₄ ClF ₄ NO ₂



262963: C31-H21-F6-N-O

SOURCE – Bayer.

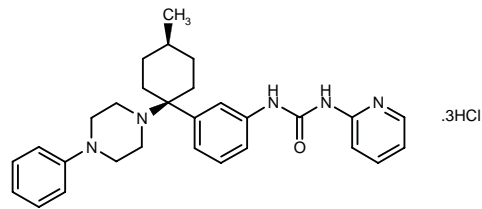
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ANTIOBESITY DRUGS

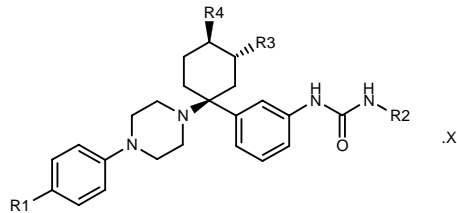
261538

cis-N-[3-[4-Methyl-1-(4-phenylpiperazin-1-yl)cyclohexyl]phenyl]-*N'*-(2-pyridyl)urea trihydrochloride



C29-H35-N5-O.3HCl; Mol wt: 579.01

ACTION – Agent for the treatment of disorders characterized by excess neuropeptide Y (NPY) such as obesity, bulimia and cardiovascular diseases including essential hypertension and congestive heart failure that selectively binds Y₁ receptors. Other specifically claimed substituted benzylamine derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
262148	H	3-Pyr	H	Me	3HCl	C ₂₉ H ₃₅ N ₅ O.3HCl
262149	H	2-Naph	H	Me	2HCl	C ₃₄ H ₃₈ N ₄ O.2HCl
262150	H	3-quinoliny	Me	H	3HCl	C ₃₃ H ₃₇ N ₅ O.3HCl
262151	F	3-quinoliny	H	Me	3HCl	C ₃₃ H ₃₆ FN ₅ O.3HCl
262152	H	4-F-Ph	H	Me	2HCl	C ₃₀ H ₃₅ FN ₄ O.2HCl
262153	H	3-quinoliny	H	Me	3HCl	C ₃₃ H ₃₇ N ₅ O.3HCl
262154	H	6-quinolyl	H	Me	3HCl	C ₃₃ H ₃₇ N ₅ O.3HCl
262155	H	3-F-Ph	H	Me	2HCl	C ₃₀ H ₃₅ FN ₄ O.2HCl

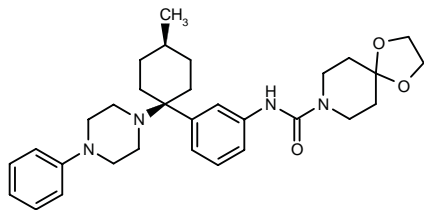
SOURCE – Neurogen.

REFERENCES

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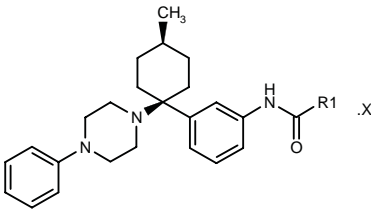
261539

cis-N-[3-[4-Methyl-1-(4-phenylpiperazin-1-yl)cyclohexyl]phenyl]-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide



C31-H42-N4-O3; Mol wt: 518.70

ACTION – Agent for the treatment of diseases characterized by excess neuropeptide Y (NPY) such as obesity, bulimia and cardiovascular diseases including essential hypertension and congestive heart failure that selectively binds to NPY Y₁ receptors. Other specifically claimed substituted benzylamine derivatives include the following:



Compound	R1	X	Formula
262143	4-oxo-1-Pip		C ₂₉ H ₃₈ N ₄ O ₂
262144	4-(MeNH)-1-Pip		C ₃₀ H ₄₃ N ₅ O
262145	4-morpholiny	2HCl	C ₂₈ H ₃₈ N ₄ O ₂ .2HCl
262146	4-Me-1-Piz	3HCl	C ₂₉ H ₄₁ N ₅ O.3HCl
262147	4-(HON=)-1-Pip	3HCl	C ₂₉ H ₃₉ N ₅ O ₂ .3HCl

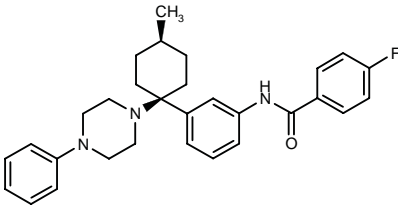
SOURCE – Neurogen.

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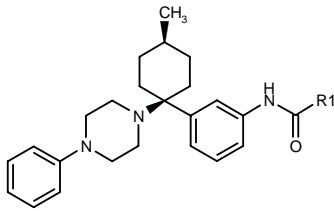
261540

cis-4-Fluoro-*N*-[3-[4-methyl-1-(4-phenylpiperazin-1-yl)cyclohexyl]phenyl]benzamide



C30-H34-F-N3-O; Mol wt: 471.62

ACTION – Neuropeptide Y₁ receptor antagonist with potential in the treatment of eating disorders such as obesity and bulimia and cardiovascular disorders such as essential hypertension and congestive heart failure. Other specifically claimed compounds from this series of benzylamine derivatives include the following:



Compound	R1	Formula
262236	4-cinnoliny	C ₃₂ H ₃₈ N ₅ O
262237	3-indazolyl	C ₃₁ H ₃₅ N ₅ O

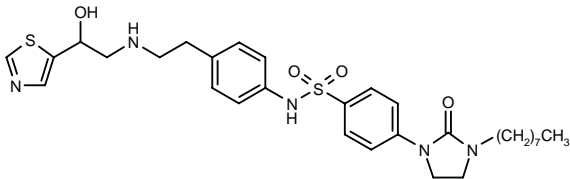
SOURCE – Neurogen.

REFERENCES

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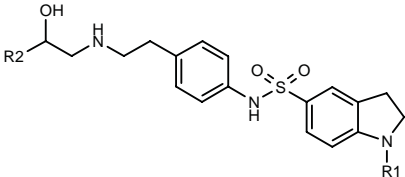
261570

N-[4-[2-[2-Hydroxy-2-(5-thiazolyl)ethylamino]ethyl]-phenyl]-4-(3-octyl-2-oxoimidazolidin-1-yl)benzenesulfonamide

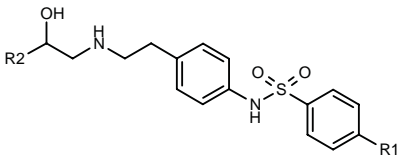


C30-H41-N5-O4-S2; Mol wt: 599.81

ACTION – Agent for the treatment of obesity and diabetes capable of increasing lipolysis and energy expenditure in cells due to its selective β_3 -adrenoceptor-agonist activity, with very little β_1 - and β_2 -adrenoceptor activity. Also reported to be capable of lowering triglyceride and cholesterol levels and increasing HDL cholesterol levels, as well as reducing intestinal motility. Within this series of specifically claimed substituted sulfonamides, the following are also included:



Compound	R1	R2	Formula
262426	4-(C8H17)-2-thiazolyl	3-Me-5-isoxazolyl	C ₃₃ H ₄₃ N ₅ O ₄ S ₂
262428	6-(C6H13)-2-Pyr	3-Me-5-isoxazolyl	C ₃₃ H ₄₁ N ₅ O ₄ S
262430	4-(C8H17)-2-thiazolyl	5-indolyl	C ₃₇ H ₄₅ N ₅ O ₃ S ₂
262434	4-(C8H17)-2-thiazolyl	furo[2,3-b]pyridin-5-yl	C ₃₆ H ₄₃ N ₅ O ₄ S ₂



Compound	R1	R2	Formula
262427	5-[3,4,5-(F)3-PhCH2]-1,2,4-oxadiazol-3-yl	3-Me-5-isoxazolyl	C ₂₉ H ₂₆ F ₃ N ₅ O ₅ S
262429	5-(C5H11)-1,2,4-oxadiazol-3-yl	3-Me-5-isoxazolyl	C ₂₇ H ₃₃ N ₅ O ₅ S
262431	3-(C6H13)-2-oxo-2,3-dihydro-1-imidazolyl	5-indolyl	C ₃₃ H ₃₉ N ₅ O ₄ S
262432	3-(C8H17)-2-oxo-1-imidazolidinyl	2,3-dihydro-1H-pyrrolo-[2,3-b]pyridin-5-yl	C ₃₄ H ₄₆ N ₆ O ₄ S
262433	3-(C8H17)-2-oxo-1-imidazolidinyl	pyrrolo[2,3-b]pyridin-5-yl	C ₃₄ H ₄₄ N ₆ O ₄ S

SOURCE – Merck & Co.

REFERENCES

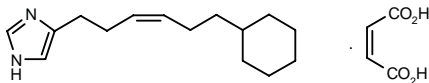
1. Fisher, M.H. et al. (Merck & Co., Inc.) *Substd. sulfonamides as selective beta3 agonists for the treatment of diabetes and obesity.* WO 9804526.

GT-2227*

262289

246227 (as free base)

4-[6-Cyclohexyl-3(Z)-hexenyl]imidazole maleate



C15-H24-N2.C4-H4-O4; Mol wt: 348.44

ACTION – Potent and selective histamine H₃ receptor antagonist, as demonstrated in binding studies by K_i values of 3.2, 13,407 and 4469 nM, respectively, for H₃, H₁ and H₂ receptors. Potentially useful for the treatment of eating disorders, sleep disorders such as narcolepsy and cognition disorders.

SOURCE – Gliatech.

REFERENCES

1. Phillips, J.G. et al. (Gliatech, Inc.) *1H-4(5)-Substd. imidazole derivs.* EP 841922, WO 9638142.

2. Handley, M.K. et al. *Synthesis of N-1 substituted derivatives of H3 receptor ligands for sensitive determinations of plasma levels in rats.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 147.

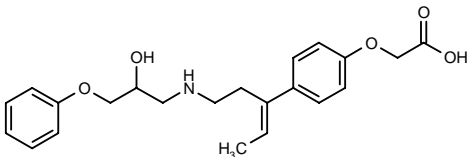
3. Tedford, C.E. *Hypothalamic histamine and regulation of appetite: Possible therapeutic implications.* IBC 5th Int Symp Ther Adv Obes (March 30-31, McLean) 1998.

*Identified compound 246227 (see 245845) Drug Data Rep 1997, 19(4): 309.

SWR-0335

262490

2-[4-[1-Ethylidene-3-(2-hydroxy-3-phenoxypropylamino)-propyl]phenoxy]acetic acid



C22-H27-N-O5; Mol wt: 385.46

ACTION – Potent β_3 -adrenoceptor agonist with selectivity over β_1 - and β_2 -adrenoceptors, potentially useful for the treatment of obesity and diabetes.

SOURCE – Sawai.

REFERENCES

1. Masagaki, T. et al. *Synthesis of novel phenoxy acetate derivatives with beta3-adrenoceptor agonist activity.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)9-43.

DIAGNOSTIC AGENTS

261564

^{99m}Tc-Annexin V-galactose

ACTION – Imaging agent, a radiolabeled annexin conjugate useful for imaging vascular thrombi, preferably those located in or near the heart.

SOURCES – NeoRx; Washington Univ., Seattle, WA (US).

REFERENCES

1. Kasina, S. et al. (NeoRx Corp.; Washington Univ.) *Radiolabeled annexins*. WO 9804294.

CHEMOKINE β-15 (HUMAN)

260143

CKβ-15

ACTION – A member of the human CC chemokine family that is expressed only in the thymus. Diagnostic methods for detecting thymus disorders and therapeutic methods for thymus-related disorders, as well as for modulating bone marrow cell proliferation and differentiation, are also provided.

SOURCE – Human Genome Sciences.

REFERENCES

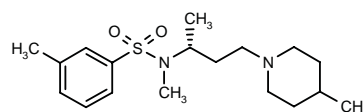
1. Wei, Y.-F. et al. (Human Genome Sci., Inc.) *Chemokine β-15*. WO 9748807.

PHARMACOLOGICAL TOOLS

SB-258719

261311

N,3-Dimethyl-*N*-[1(*R*)-methyl-3-(4-methyl-1-piperidinyl)-propyl]benzenesulfonamide



C18-H30-N2-O2-S; Mol wt: 338.51

ACTION – The first selective 5-HT₇ receptor antagonist with a profile consistent with competitive antagonism, displacing [³H]-5-CT binding to cloned human receptors expressed in HEK 293 cells with a pK_i of 7.5 ± 0.04; it is at least 100-fold more selective over a range of other receptors such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT_{1F} and 5-HT₄ receptors, α_{1B}-adrenoceptors and dopamine D₂ and D₃ receptors. The 5-HT₇ receptor-antagonist properties of the compound were demonstrated by inhibition of 5-CT-induced adenylyl cyclase activity in HEK 293 cell membranes stably expressing the cloned human 5-HT₇ receptor (pK_B = 7.0 ± 0.1), whereas it exhibited no agonist activity. Potentially useful as a tool for elucidating the biological role of 5-HT₇ receptors in the CNS and the periphery.

SOURCE – SmithKline Beecham.

REFERENCES

1. Forbes, I.T. (SmithKline Beecham plc) *Sulfonamide derivs. as 5HT₇ receptor antagonists*. WO 9729097.
2. Forbes, I.T. et al. (*R*)-3,*N*-Dimethyl-*N*-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]-benzene sulfonamide: The first selective 5-HT₇ receptor antagonist. *J Med Chem* 1998, 41(5): 655 (Letters to the Editor).

DIAGNOSTIC AGENTS

261564

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REFERENCES

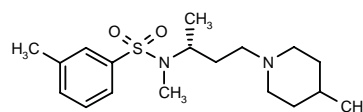
1. Wei, Y.-F. et al. (Human Genome Sci., Inc.) *Chemokine β -15*. WO 9748807.

PHARMACOLOGICAL TOOLS

SB-258719

261311

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SOURCE – SmithKline Beecham.

REFERENCES

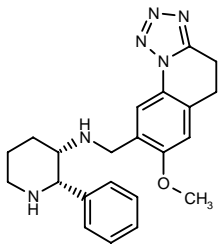
1. Forbes, I.T. (SmithKline Beecham plc) *Sulfonamide derivs. as 5HT₇ receptor antagonists*. WO 9729097.
2. Forbes, I.T. et al. (*R*)-3,*N*-Dimethyl-*N*-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]-benzene sulfonamide: The first selective 5-HT₇ receptor antagonist. *J Med Chem* 1998, 41(5): 655 (Letters to the Editor).

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

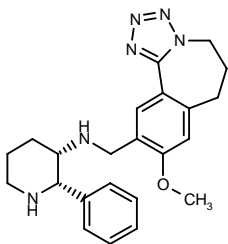
262086

(2*S*,3*S*)-3-(7-Methoxy-4,5-dihydro[1,2,3,4]tetrazolo-[1,5-*a*]quinolin-8-ylmethylamino]-2-phenylpiperidine

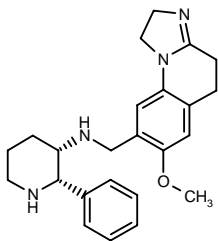


C22-H26-N6-O; Mol wt: 390.49

ACTION – Analgesic and antiinflammatory agent, a substance P (NK₁ receptor) antagonist. Other specifically claimed piperidinylamino tricyclic compounds include the following:



262881: C23-H28-N6-O



262882: C24-H30-N4-O

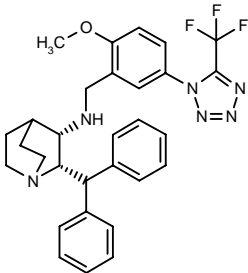
SOURCE – Pfizer.

REFERENCES

1. Koike, H. and Wakabayashi, H. (Pfizer, Inc.) *Piperidinylamino tricyclic opds. as substance P antagonists*. EP 824100, JP 98072464.

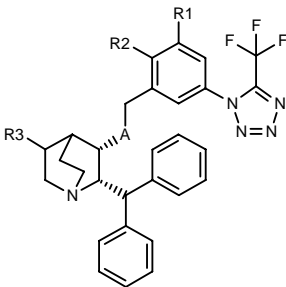
262116

(2*S*,3*S*)-2-(Diphenylmethyl)-3-[2-methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]benzylamino]quinuclidine



C30-H31-F3-N6-O; Mol wt: 548.61

ACTION – Analgesic and antiinflammatory agent, a substance P (NK₁ receptor) antagonist. Other specifically claimed tetrazolyl-substituted quinuclidines include the following:



Compound	R1	R2	R3	A	Isomer	Formula
262853	H	OMe	CO ₂ H	NH	4 <i>S</i> ,5 <i>R</i>	C ₃₁ H ₃₁ F ₃ N ₆ O ₃
262854	H	OMe	CO ₂ H	NH	4 <i>R</i> ,5 <i>S</i>	C ₃₁ H ₃₁ F ₃ N ₆ O ₃
262855	CF ₃	H	H	NH		C ₃₀ H ₂₈ F ₆ N ₆
262856	CF ₃	H	CO ₂ H	NH	4 <i>S</i> ,5 <i>R</i>	C ₃₁ H ₂₈ F ₆ N ₆ O ₂
262857	CF ₃	H	CO ₂ H	NH	4 <i>R</i> ,5 <i>S</i>	C ₃₁ H ₂₈ F ₆ N ₆ O ₂
262858	CF ₃	H	H	O		C ₃₀ H ₂₇ F ₆ N ₆ O
262859	CF ₃	H	CO ₂ H	O	4 <i>S</i> ,5 <i>R</i>	C ₃₁ H ₂₇ F ₆ N ₆ O ₃
262860	CF ₃	H	CO ₂ H	O	4 <i>R</i> ,5 <i>S</i>	C ₃₁ H ₂₇ F ₆ N ₆ O ₃

SOURCE – Pfizer.

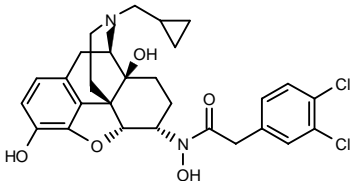
REFERENCES

1. Satake, K. (Pfizer, Inc.) *Tetrazolyl-substd. quinuclidines as substance P antagonists*. EP 829480, JP 98087661.

262117

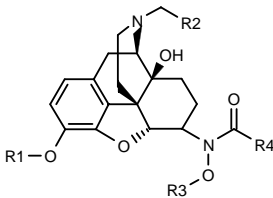
N-[17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14 β -dihydroxymorphinan-6 α -yl]-2-(3,4-dichlorophenyl)acetohydroxamic acid

N-[17-(Cyclopropylmethyl)-4,5 α -epoxy-3,14 β -dihydroxymorphinan-6 α -yl]-2-(3,4-dichlorophenyl)-*N*-hydroxyacetamide



C28-H30-Cl2-N2-O5; Mol wt: 545.46

ACTION – Analgesic agent that exhibits good binding affinity for the opioid receptor-like (ORL1) receptor, as well as significant agonist activity at opioid receptors. Also claimed for use as an antiinflammatory, diuretic, anesthetic and neuroprotective agent. Other specifically claimed morphinan hydroxamic acid compounds include the following:



Compound	R1	R2	R3	R4	Formula
262899	H	cyclopropyl	Me	3,4-(Cl)2-PhCH2	C ₂₉ H ₃₂ Cl ₂ N ₂ O ₅
263564	H	cyclopropyl	H	3,4-(Cl)2-PhCH2	C ₂₈ H ₃₀ Cl ₂ N ₂ O ₅
263565	H	cyclopropyl	Me	3,4-(Cl)2-PhCH2	C ₂₉ H ₃₂ Cl ₂ N ₂ O ₅
263566	Me	cyclopropyl	Me	3,4-(Cl)2-PhCH2	C ₃₀ H ₃₄ Cl ₂ N ₂ O ₅
263567	H	vinyl	Me	3,4-(Cl)2-PhCH2	C ₂₈ H ₃₀ Cl ₂ N ₂ O ₅
263568	H	cyclopropyl	Me	3,4-(Cl)2-Ph	C ₂₈ H ₃₀ Cl ₂ N ₂ O ₅
263569	H	cyclopropyl	Me	3,4-(Cl)2-PhCH=CH	C ₃₀ H ₃₂ Cl ₂ N ₂ O ₅
263570	H	vinyl	Me	2-furyl	C ₂₈ H ₂₈ N ₂ O ₆

SOURCE – Pfizer.

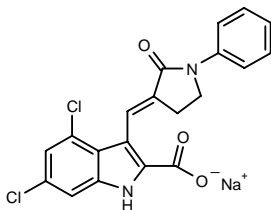
REFERENCES

1. Ito, F. (Pfizer, Inc.) *Morphinan hydroxamic acid cpds*. EP 829481, JP 98087667.

GV-196771A*

225789

(*E*)-4,6-Dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidenemethyl)-1*H*-indole-2-carboxylic acid sodium salt



C20-H13-Cl2-N2-Na-O3; Mol wt: 423.23

ACTION – Antinociceptive agent for the treatment of chronic pain, an NMDA receptor antagonist with high affinity for the glycine site ($pK_i = 7.56 \pm 0.09$) and high potency in blocking glycine-induced ion currents in the presence of NMDA in spinal cord ($pK_B = 8.04$) and cortical neurons ($pK_B = 7.53$) from embryonic rats. Compound demonstrated antihyperalgesic effects in an acute inflammatory model in mice (formalin test) at doses of 0.1-10 mg/kg p.o. It was also active in a model of painful mononeuropathy in rats (chronic constriction injury of the left sciatic nerve), preventing the development of thermal hyperalgesia at 3 mg/kg p.o. twice a day, and reversing hyperalgesia for up to 8 h after administration in animals with established thermal hypersensitivity ($ED_{50} = 2.95$ mg/kg p.o.).

SOURCE – Glaxo Wellcome.

REFERENCES

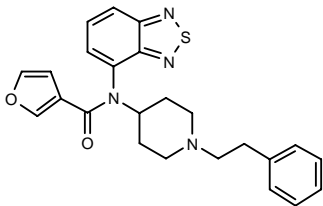
- Cugola, A. et al. (Glaxo SpA) *Indole derivs. as NMDA antagonists*. EP 723541, JP 97503770, US 5760059, WO 9510517.
- Quartaroli, M. et al. *Antinociceptive activity of a novel NMDA receptor glycine antagonist: GV196771A*. Soc Neurosci Abst 1997, 23(Part 1): Abst 375.21.
- Glaxo Wellcome development pipeline*. Prous Science Daily Essentials February 28, 1997.
- Glaxo Wellcome's R&D pipeline remains full and diverse*. Prous Science Daily Essentials January 21, 1998.
- Glaxo Wellcome Annual Report 1996.

*Identified compound **225789** (see **224170**) Drug Data Rep 1995, 17(9): 801.

OHM-3507*

146846

N-(Benzo-2,1,3-thiadiazol-4-yl)-*N*-[1-(2-phenylethyl)-4-piperidyl]furan-3-carboxamide



C24-H24-N4-O2-S; Mol wt: 432.54

ACTION – Analgesic agent structurally related to fentanyl that displays high affinity for μ -receptors ($IC_{50} = 10$ nM) and less binding affinity for δ - (6-fold lower) and κ - (176-fold lower) receptors. Although OHM-3507 appeared to have low-efficacy opioid effects in nonprimate species, in rhesus monkeys it displayed strong fentanyl-like μ -agonist activity, as demonstrated by morphine-like discriminative stimulus effects and antinociceptive effects in a model of tail-withdrawal latencies in warm water ($ED_{50} = 0.14$ mg/kg s.c.); in addition, it decreased ventilation in monkeys breathing normal air or 5% CO₂, without significantly altering accuracy on acquisition and performance tasks at doses decreasing responding.

SOURCE – Ohmeda (now Baxter).

REFERENCES

1. Bagley, J.R. and Spencer, K.H. (The BOC Group) *N-Heterocyclic-N-(4-piperidyl)amides*. AU 8811142, EP 227794, JP 88264460, US 4791112.

2. France, C.P. et al. *Behavioral effects and binding affinities of the fentanyl derivative OHM3507*. Pharmacol Biochem Behav 1998, 59(2): 295.

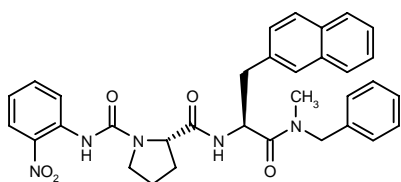
*Identified compound **146846** (see **146006**) Drug Data Rep 1995, 17(5): 410.

SDZ-NKT-343*

239014

N-(2-Nitrophenyl)carbamoyl-L-prolyl-L-[3-(2-naphthyl)]-alanine *N*-benzyl-*N*-methanamide

NKT-343



C33-H33-N5-O5; Mol wt: 579.65

ACTION – Potent, long-acting, orally active analgesic agent, a reversible, noncompetitive tachykinin antagonist with selectivity for human NK₁ receptors (IC₅₀ = 0.62 nM) over human NK₂ and NK₃ receptors (K_i = 0.52 and 3.4 μM, respectively) and rat NK₁ receptors (IC₅₀ = 451 nM); it was only weakly active against voltage-activated Ca²⁺ and Na⁺ channels. Compound inhibited [Sar⁹]-substance P sulfone-induced contractions in guinea pig ileum (IC₅₀ = 1.60 nM) and in gerbil urinary bladder (IC₅₀ = 1.10 nM). In anesthetized guinea pigs, it inhibited bronchoconstriction evoked by [Sar⁹]-substance P sulfone with an IC₅₀ of 0.08 mg/kg i.v. at 10 min and 1.0 mg/kg i.v. at 60 min. In models of chronic carrageenan-induced inflammatory pain and neuropathic pain induced by partial ligation of the left sciatic nerve in guinea pigs, it displayed potent oral analgesic activity, with ED₃₀ values of 1.1 and 0.02 mg/kg, respectively, at 3 h. Currently in early clinical trials.

SOURCE – Novartis.

REFERENCES

1. Ko, S.Y. and Walpole, C. (Sandoz, Ltd.; Sandoz-Patent GmbH; Sandoz-Erfindungen VmbH; Sandoz Pharm., Ltd.) *Tachykinin antagonists*. EP 797583, WO 9618643.

2. Gentry, C. et al. *The selective NK-1 receptor antagonist SDZ NKT 343 inhibits both inflammatory and neuropathic hyperalgesia in the guinea pig*. Brit J Pharmacol 1998, 123(Suppl.): Abstr 221P.

3. Walpole, C.S.J. et al. *SDZ NKT 343 - Potent human NK-1 receptor antagonist with good oral analgesic activity in chronic pain models*. Int Tachykinin Conf: Tachykinins Health Dis (Sept 7-11, Cairns) 1997, 4.

4. Walpole, C.S.J. et al. *Comparative, general pharmacology of SDZ NKT 343, a novel, selective NK1 receptor antagonist*. Brit J Pharmacol 1998, 124(1): 83.

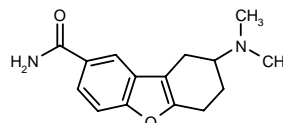
5. Novartis Pharma Res Dev Present Financial Commun (June 17, Basel/June 18, East Hanover) 1997.

*Identified compound **239014** Drug Data Rep 1996, 18(10): 863.

ANTIMIGRAINE DRUGS

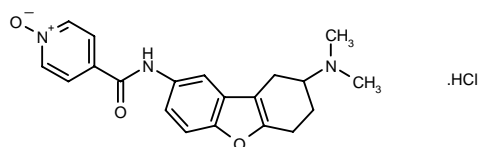
263320

2-(Dimethylamino)-1,2,3,4-tetrahydrodibenzofuran-8-carboxamide



C22-H21-Cl-N2-O2; Mol wt: 258.32

ACTION – Agent for the treatment or prevention of migraine with 5-HT_{1F}-agonist activity. Another compound from this series of substituted benzofurans is:



264319: C20-H21-N3-O3.HCl

SOURCE – Lilly.

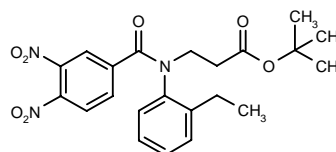
REFERENCES

1. Flaugh, M.E. and Kiefer, J.A.D. (Eli Lilly & Co.) *Subst. 1,2,3,4-tetrahydro-2-dibenzofuranamines and 2-aminocyclohepta[b]benzofurans*. WO 9808502.

263779

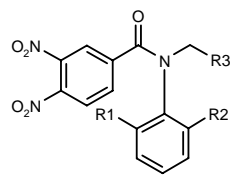
N-[2-(*tert*-Butoxycarbonyl)ethyl]-*N*-(2-ethylphenyl)-3,4-dinitrobenzamide

3-[*N*-(3,4-Dinitrobenzoyl)-*N*-(2-ethylphenyl)amino]-propionic acid *tert*-butyl ester



C22-H25-N3-O7; Mol wt: 443.46

ACTION – Calcitonin gene-related peptide (CGRP) receptor antagonist with potential in the treatment or prevention of disease states mediated by CGRP including headache, especially migraine, and non-insulin-dependent diabetes, neurogenic inflammation, cardiovascular disorders, chronic inflammation, pain, endotoxic shock, arthritis, allergic rhinitis, contact dermatitis, inflammatory skin conditions and asthma. Other specifically claimed compounds from this series of 3,4-dinitrobenzamides include the following:



Compound	R1	R2	R3	Formula
264919	Et	H	CH2CON(Et)2	C ₂₂ H ₂₆ N ₄ O ₆
264920	Et	H	CH2COPh	C ₂₄ H ₂₁ N ₃ O ₆
264921	Et	Et	H	C ₁₈ H ₁₉ N ₃ O ₅
264922	H	H	2,3,4,5-tetrahydro-1H-3-benzazepin-3-yl-CH2CH2	C ₂₆ H ₂₆ N ₄ O ₅
264923	H	H	CH2CH2N(Me)CH2CH2Ph	C ₂₅ H ₂₆ N ₄ O ₅
264924	H	H	CH2N(Me)2	C ₁₇ H ₁₈ N ₄ O ₅

SOURCE – SmithKline Beecham.

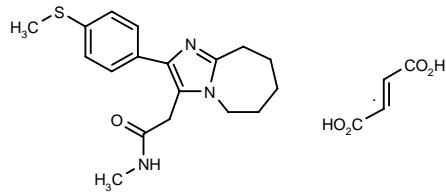
REFERENCES

1. Daines, R.A. (SmithKline Beecham Corp.) *Cpds. and methods*. WO 9809630.

ANESTHETIC DRUGS

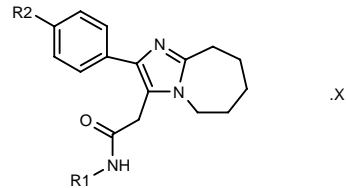
262925

N-Methyl-2-[2-[4-(methylsulfonyl)phenyl]-6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*]azepin-3-yl]acetamide fumarate



C18-H23-N3-O-S.C4-H4-O4; Mol wt: 445.53

ACTION – Anesthetic, sedative/hypnotic and anti-convulsant with high affinity for the ω_1 and ω_2 (benzodiazepine) recognition sites within the GABA_A receptor complex and agonist activity at these receptors. A representative compound from a series of 6,7,8,9-tetrahydro-5*H*-imidazo[1,2-*a*]azepine-3-acetic acid derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
263180	Et	SMe	fumarate	C ₁₉ H ₂₅ N ₃ OS.C ₄ H ₄ O ₄
263181	Me	SOMe		C ₁₈ H ₂₃ N ₃ O ₂ S
263182	Et	SOMe		C ₁₉ H ₂₅ N ₃ O ₂ S
263183	Et	SO2Me		C ₁₉ H ₂₅ N ₃ O ₃ S

SOURCE – Synthélabo.

REFERENCES

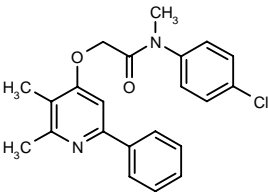
1. De Peretti, D. et al. (Synthélabo) 6,7,8,9-Tetrahydro-5*H*-imidazo[1,2-*a*]azepine-3-acetic acid derivs., preparation thereof and therapeutical use thereof. WO 9805664.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

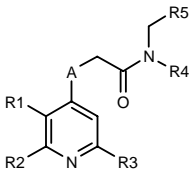
262819

N-(4-Chlorophenyl)-2-(2,3-dimethyl-6-phenylpyridin-4-yloxy)-*N*-methylacetamide



C22-H21-Cl-N2-O2; Mol wt: 380.87

ACTION – Potent and selective ligand for the benzodiazepine ω_3 receptor subtype (IC₅₀ = 1.0 nM) with much weaker affinity for ω_1 and ω_2 receptor subtypes (IC₅₀ > 1000 nM for both). Potentially useful for the treatment of anxiety, depression and epilepsy. Other compounds from this series of pyridine derivatives include the following:

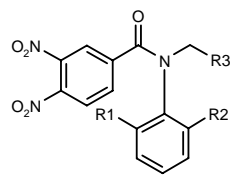


Compound	R1	R2	R3	R4	R5	A	Formula
263073	Me	Me	Ph	Pr	Et	O	C ₂₁ H ₂₈ N ₂ O ₂
263074	-(CH2)4-		4-Cl-Ph	Pr	Et	O	C ₂₃ H ₂₉ ClN ₂ O ₂
263075	Me	Me	Ph	4-Cl-Ph	H	NH	C ₂₂ H ₂₂ ClN ₃ O
263076	-(CH2)4-		Ph	4-Cl-Ph	H	NH	C ₂₄ H ₂₄ ClN ₃ O
263077	-(CH2)4-		2-Me-3-furyl	4-Cl-Ph	H	O	C ₂₃ H ₂₃ ClN ₂ O ₃

SOURCE – Dainippon.

REFERENCES

1. Murata, A. and Furukawa, K. (Dainippon Pharm. Co., Ltd.) *Pyridine derivs.* JP 98072439.



Compound	R1	R2	R3	Formula
264919	Et	H	CH2CON(Et)2	C ₂₂ H ₂₆ N ₄ O ₆
264920	Et	H	CH2COPh	C ₂₄ H ₂₁ N ₃ O ₆
264921	Et	Et	H	C ₁₈ H ₁₉ N ₃ O ₅
264922	H	H	2,3,4,5-tetrahydro-1H-3-benzazepin-3-yl-CH2CH2	C ₂₆ H ₂₆ N ₄ O ₅
264923	H	H	CH2CH2N(Me)CH2CH2Ph	C ₂₅ H ₂₆ N ₄ O ₅
264924	H	H	CH2N(Me)2	C ₁₇ H ₁₈ N ₄ O ₅

SOURCE – SmithKline Beecham.

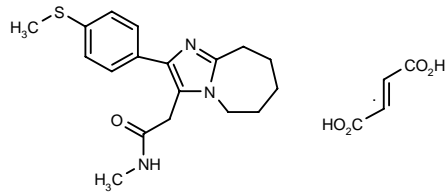
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1. Daines, R.A. (SmithKline Beecham Corp.) *Cpds. and methods*. WO 9809630.

ANESTHETIC DRUGS

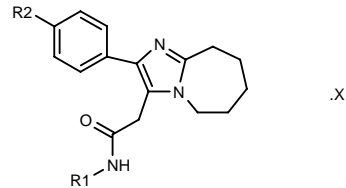
262925

N-Methyl-2-[2-[4-(methylsulfonyl)phenyl]-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepin-3-yl]acetamide fumarate



C18-H23-N3-O-S.C4-H4-O4; Mol wt: 445.53

ACTION – Anesthetic, sedative/hypnotic and anti-convulsant with high affinity for the ω_1 and ω_2 (benzodiazepine) recognition sites within the GABA_A receptor complex and agonist activity at these receptors. A representative compound from a series of 6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine-3-acetic acid derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
263180	Et	SMe	fumarate	C ₁₉ H ₂₅ N ₃ OS.C ₄ H ₄ O ₄
263181	Me	SOMe		C ₁₈ H ₂₃ N ₃ O ₂ S
263182	Et	SOMe		C ₁₉ H ₂₅ N ₃ O ₂ S
263183	Et	SO2Me		C ₁₉ H ₂₅ N ₃ O ₃ S

SOURCE – Synthélabo.

REFERENCES

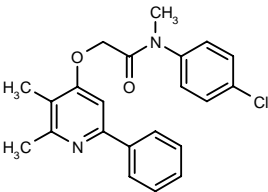
1. De Peretti, D. et al. (Synthélabo) 6,7,8,9-Tetrahydro-5H-imidazo[1,2-a]azepine-3-acetic acid derivs., preparation thereof and therapeutical use thereof. WO 9805664.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

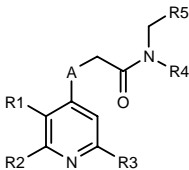
262819

N-(4-Chlorophenyl)-2-(2,3-dimethyl-6-phenylpyridin-4-yloxy)-N-methylacetamide



C22-H21-Cl-N2-O2; Mol wt: 380.87

ACTION – Potent and selective ligand for the benzodiazepine ω_3 receptor subtype (IC₅₀ = 1.0 nM) with much weaker affinity for ω_1 and ω_2 receptor subtypes (IC₅₀ > 1000 nM for both). Potentially useful for the treatment of anxiety, depression and epilepsy. Other compounds from this series of pyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
263073	Me	Me	Ph	Pr	Et	O	C ₂₁ H ₂₈ N ₂ O ₂
263074	-(CH2)4-		4-Cl-Ph	Pr	Et	O	C ₂₃ H ₂₉ ClN ₂ O ₂
263075	Me	Me	Ph	4-Cl-Ph	H	NH	C ₂₂ H ₂₂ ClN ₃ O
263076	-(CH2)4-		Ph	4-Cl-Ph	H	NH	C ₂₄ H ₂₄ ClN ₃ O
263077	-(CH2)4-		2-Me-3-furyl	4-Cl-Ph	H	O	C ₂₃ H ₂₃ ClN ₂ O ₃

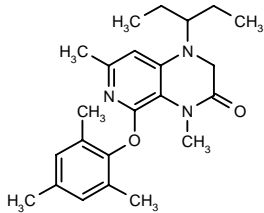
SOURCE – Dainippon.

REFERENCES

1. Murata, A. and Furukawa, K. (Dainippon Pharm. Co., Ltd.) *Pyridine derivs.* JP 98072439.

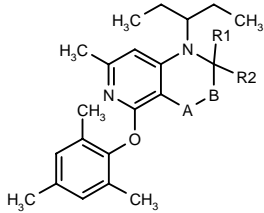
262924

1-(1-Ethylpropyl)-4,7-dimethyl-5-(2,4,6-trimethylphenoxy)-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-3-one

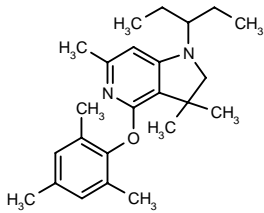


C23-H31-N3-O2; Mol wt: 381.52

ACTION – Corticotropin-releasing factor (CRF) antagonist with potential in the treatment of a wide range of disorders such as anxiety, depression, headache, irritable bowel syndrome, inflammatory disorders, Alzheimer’s disease, gastrointestinal disorders, eating disorders, hemorrhagic stress, drug and alcohol withdrawal symptoms, infertility, stroke and stress-induced infections. Other specifically claimed compounds from this series of bicyclic pyridine or pyrimidine derivatives include the following:



Compound	R1	R2	A	B	Formula
263573	H	H	N(Me)	CH2	C ₂₃ H ₃₃ N ₃ O
263574	H	H	NH	CH2	C ₂₂ H ₃₁ N ₃ O
263575		-O-	CH2	CH(CO2Me)	C ₂₈ H ₃₂ N ₂ O ₄
263576		-O-	CH2	CH(CO2-i-Pr)	C ₂₇ H ₃₆ N ₂ O ₄
263577		-O-	CH2	CH2	C ₂₃ H ₃₀ N ₂ O ₂
263578	H	H	CH2	CH2	C ₂₃ H ₃₂ N ₂ O
263579	H	H	CH2	O	C ₂₂ H ₃₀ N ₂ O ₂
263580	H	H	CH(Me)	O	C ₂₃ H ₃₂ N ₂ O ₂



263581: C24-H34-N2-O

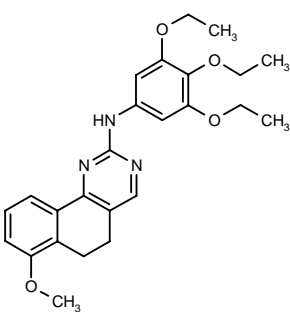
SOURCE – Pfizer.

REFERENCES

1. Chen, Y.L. (Pfizer, Inc.) *Substd. pyrido- or pyrimido-containing 6,6- or 6,7-bicyclic derivs.* WO 9805661.

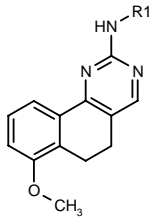
263742

N-(7-Methoxy-5,6-dihydrobenzo[*h*]quinazolin-2-yl)-*N*-(3,4,5-triethoxyphenyl)amine



C25-H29-N3-O4; Mol wt: 435.52

ACTION – Agent for the treatment of anxiety, panic, obsessive-compulsive disorder, alcoholism, depression, migraine, sleep disorders, eating disorders and priapism, a selective 5-HT_{2C} receptor antagonist. Other specifically claimed compounds from this series of pyrimidine derivatives include the following:



Compound	R1	Formula
263931	3,5-(MeO)2-4-EtO-Ph	C ₂₃ H ₂₅ N ₃ O ₄
263932	1-Me-5-indolyl	C ₂₂ H ₂₀ N ₄ O

SOURCE – Syntex (Roche).

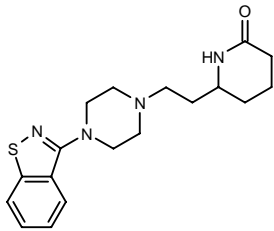
REFERENCES

1. Flippin, L.A. and Weatherhead, G.S. (Syntex [USA], Inc.) *Pyrimidine derivs.* US 5753663.

ANTIPSYCHOTIC DRUGS

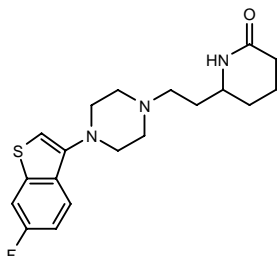
258426

6-[2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl]ethyl]-piperidin-2-one



C18-H24-N4-O-S; Mol wt: 344.47

ACTION – Antipsychotic agent with potent binding affinity for dopamine D₂ receptors (57.8% inhibition of [³H]-spiperone binding at 0.1 μM in rat striatum preparations) and 5-HT₂ receptors (52.5% inhibition of [³H]-ketanserin binding in rat cortex preparations at 0.01 μM). Another representative compound within this series of piperidone and homo-piperidone derivatives is:



263148: C19-H24-F-N3-O-S

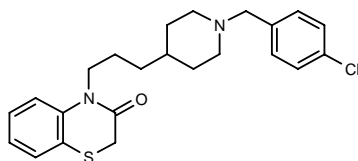
SOURCE – Meiji Seika.

REFERENCES

1. Kikuchi, C. et al. (Meiji Seika Kaisha, Ltd.) *Piperidinone and homopiperidinone derivs.* JP 97291090.

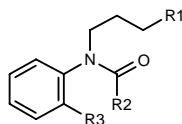
263295

4-[3-[1-(4-Chlorobenzyl)piperidin-4-yl]propyl]-3,4-dihydro-2H-1,4-benzothiazin-3-one



C23-H27-Cl-N2-O-S; Mol wt: 414.99

ACTION – Antipsychotic agent that acts by virtue of its dopamine D₄ receptor-antagonist activity (K_i = 1.0 nM against [³H]-spiperone binding in cell membranes expressing human cloned D₄ receptors). No toxic effects were observed in mice after a single dose of 32 mg/kg i.p. Within this series of quinoline derivatives, the following are also included:



Compound	R1	R2,R3	Formula
263755	4-(4-Cl-PhO)-1-Pip	-CH=CH-	C ₂₃ H ₂₅ ClN ₂ O ₂
263756	1-(4-Cl-PhCH ₂)-4-Pip	-(CH ₂) ₂ -	C ₂₄ H ₂₉ ClN ₂ O
263757	1-(2-Me-PhCH ₂)-4-Pip	-(CH ₂) ₂ -	C ₂₅ H ₃₂ N ₂ O
263758	1-(4-Me-PhCH ₂)-4-Pip	-(CH ₂) ₂ -	C ₂₅ H ₃₂ N ₂ O

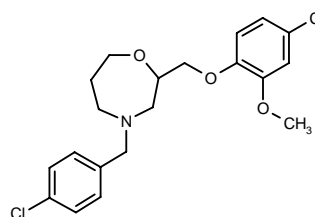
SOURCE – Meiji Seika.

REFERENCES

1. Hasegawa, T. et al. (Meiji Seika Kaisha, Ltd.) *Quinoline derivs. and psychotropic agent.* WO 9807703.

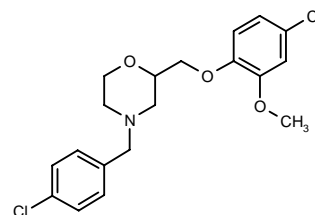
263299

(±)-4-(4-Chlorobenzyl)-2-(4-chloro-2-methoxyphenoxy-methyl)perhydro-1,4-oxazepine



C20-H23-Cl2-N-O3; Mol wt: 396.31

ACTION – Antipsychotic agent, a potent and selective dopamine D₄ receptor antagonist, as demonstrated in binding assays (IC₅₀ = 2.5 nM and > 10.00 μM, respectively, against [³H]-spiperone binding to human D₄ and D₂ receptors cloned in CHO cells). Another specifically claimed compounds from this series of disubstituted morpholine, oxazepine or thiazepine derivatives is:



264009: C19-H21-Cl2-N-O3

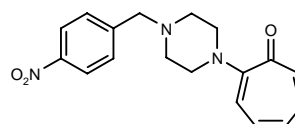
SOURCE – NeuroSearch.

REFERENCES

1. Axelsson, O. et al. (NeuroSearch A/S) *Disubstd. morpholine, oxazepine or thiazepine derivs., their preparation and their use as dopamine D₄ receptor antagonists.* WO 9807710.

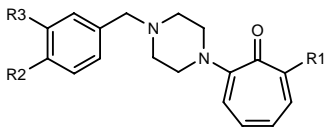
263300

2-[4-(4-Nitrobenzyl)piperazin-1-yl]-2,4,6-cycloheptatrien-1-one



C18-H19-N3-O3; Mol wt: 325.37

ACTION – Antipsychotic agent, a potent and selective dopamine D₄ receptor antagonist (K_i = 6.67 nM) with 1014-fold selectivity over D₂ receptors. Antagonist activity was demonstrated by reversal of dopamine inhibition of forskolin-stimulated adenylyl cyclase activity in CHO cells transfected with the human D₄ receptor (32% reversal at 1 μM and 65% at 10 μM). Other specifically claimed compounds within this series of troponylpiperazines include the following:



Compound	R1	R2	R3	Formula
263909	H	-OCH2O-		C ₁₉ H ₂₀ N ₂ O ₃
263910	H	Br	H	C ₁₈ H ₁₉ BrN ₂ O
263911	H	CF3	H	C ₁₉ H ₁₉ F ₃ N ₂ O
263912	H	OCF3	H	C ₁₉ H ₁₉ F ₃ N ₂ O ₂
263913	H	Cl	H	C ₁₈ H ₁₉ ClN ₂ O
263914	Br	-OCH2O-		C ₁₉ H ₁₈ BrN ₂ O ₃
263915	H	-CH=CHCH=CH-		C ₂₂ H ₂₂ N ₂ O

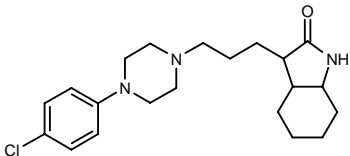
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Fu, J.-M. et al. (Hoechst Marion Roussel, Inc.) *Troponyl piperazines as selective dopamine D4 receptor ligands*. WO 9807711.

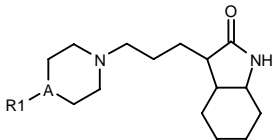
263340

3-[3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl]-perhydroindol-2-one

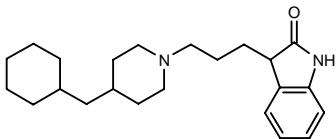


C21-H30-Cl-N3-O; Mol wt: 375.94

ACTION – Antipsychotic agent with potent affinity for dopamine D₄ receptors (K_i = 1.0 nM against [³H]-spiperone binding to cloned human D₄ receptors). No toxicity was observed following i.p. administration of 32 mg/kg to mice. Other compounds from this series of oxindoles include the following:



Compound	R1	A	Formula
264013	1,2-benzisothiazol-3-yl-CH2	CH	C ₂₄ H ₃₃ N ₃ OS
264014	Ph	N	C ₂₁ H ₃₁ N ₃ O
264015	3-Cl-Ph	N	C ₂₁ H ₃₀ ClN ₃ O



264012: C23-H34-N2-O

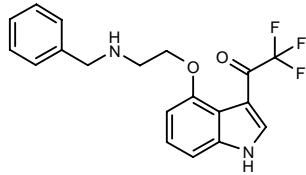
SOURCE – Meiji Seika.

REFERENCES

1. Hasegawa, T. et al. (Meiji Seika Kaisha, Ltd.) *Oxindole derivs. and psychotropic drugs*. WO 9808816.

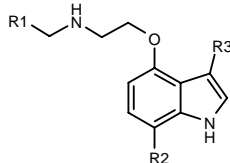
263341

1-[4-[2-(Benzylamino)ethoxy]-1*H*-indol-3-yl]-2,2,2-trifluoroethanone



C19-H17-F3-N2-O2; Mol wt: 362.35

ACTION – Antipsychotic agent that acts as a dopamine autoreceptor agonist (IC₅₀ = 5.93 nM against [³H]-quinpirole binding in rat striatal tissue), with reduced affinity for postsynaptic dopamine D₂ receptors (IC₅₀ = 286 nM using [³H]-spiperidol as the ligand in rat limbic tissue); it also possesses good affinity for 5-HT_{1A} receptors (IC₅₀ = 60 nM) and may therefore be useful as an anxiolytic and antidepressant agent. Other specifically claimed 4-aminoethoxy indoles include the following:



Compound	R1	R2	R3	Formula
264140	(CH2)3Ph	H	H	C ₂₀ H ₂₄ N ₂ O
264141	Ph	Cl	H	C ₁₇ H ₁₇ ClN ₂ O
264142	Ph	Cl	Cl	C ₁₇ H ₁₆ Cl ₂ N ₂ O
264143	4-F-Ph	Cl	Cl	C ₁₇ H ₁₅ Cl ₂ FN ₂ O
264144	4-Cl-Ph	Cl	Cl	C ₁₇ H ₁₅ Cl ₃ N ₂ O
264145	2-thienyl	Cl	Cl	C ₁₅ H ₁₄ Cl ₂ N ₂ OS
264146	(CH2)3Ph	H	Cl	C ₂₀ H ₂₃ ClN ₂ O
264147	Ph	Cl	COCF3	C ₁₉ H ₁₆ ClF ₃ N ₂ O ₂
264148	Ph	H	H	C ₁₇ H ₁₈ N ₂ O

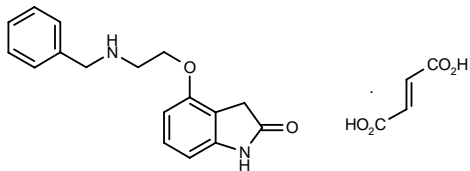
SOURCE – American Home Products.

REFERENCES

1. Mewshaw, R.E. and Webb, M.B. (American Home Prods. Corp.) *4-Aminoethoxy indoles as dopamin D₂ agonists and as 5HT_{1A} ligands*. WO 9808817.

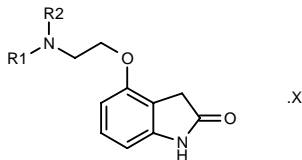
263343

4-[2-(Benzylamino)ethoxy]indolin-2-one fumarate



C17-H18-N2-O2.C4-H4-O4; Mol wt: 398.41

ACTION – Antipsychotic agent that acts as a dopamine autoreceptor agonist (IC_{50} = 0.41 nM against [3H]-quinpirole binding in rat striatal tissue), with reduced affinity for postsynaptic dopamine D_2 receptors (IC_{50} = 145 nM using [3H]-spiroperidol in rat limbic tissue). Also potentially useful for the treatment of Parkinson’s disease. Within this series of specifically claimed 4-aminoethoxy indolone derivatives, the following are also included:



Compound	R1	R2	X	Formula
264276	H	Me	fumarate	$C_{11}H_{14}N_2O_2 \cdot C_4H_4O_4$
264277	H	H		$C_{10}H_{12}N_2O_2$
264278	CH ₂ Ph	Me	fumarate H ₂ O	$C_{18}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot H_2O$
264279	3-Me-PhCH ₂	3-Me-PhCH ₂	fumarate	$C_{26}H_{28}N_2O_2 \cdot C_4H_4O_4$

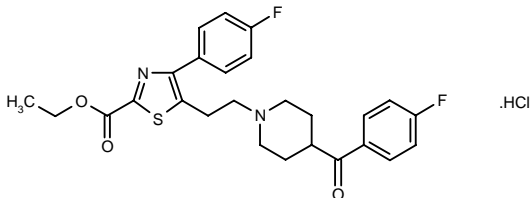
SOURCE – American Home Products.

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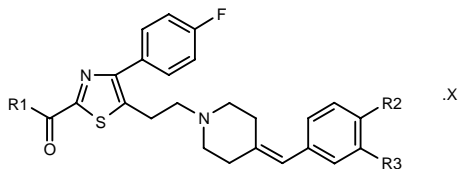
263889

5-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-4-(4-fluorophenyl)thiazole-2-carboxylic acid ethyl ester hydrochloride



C26-H26-F2-N2-O3-S.HCl; Mol wt: 521.02

ACTION – Agent for the treatment of disorders such as schizophrenia, cerebrovascular disorders and senile dementia, a potent and selective dopamine D_4 receptor antagonist (IC_{50} = 3.43 nM against [3H]-spiperone binding to human receptors expressed in CHO cells) with low potential for inducing extrapyramidal side effects due to its low affinity for dopamine D_2 receptors (IC_{50} > 1000 nM). Within this series of 2-carbonylthiazole derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
264710	NH ₂	F	H		$C_{24}H_{23}F_2N_3OS$
264711	OE _t	H	F	HCl	$C_{26}H_{26}F_2N_2O_2S \cdot HCl$
264713	OK	H	F		$C_{24}H_{21}F_2KN_2O_2S$
264714	NH ₂	H	H		$C_{24}H_{24}FN_3OS$

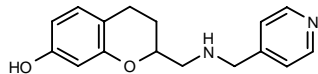
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharm. Co., Ltd.; Nihon Nohyaku Co., Ltd.) 2-Carbonylthiazole derivs. and use of the same. WO 9812195.

264051

2-(4-Pyridylmethylaminomethyl)-3,4-dihydro-2H-1-benzopyran-7-ol



C16-H18-N2-O2; Mol wt: 270.33

ACTION – Antipsychotic agent reported to be free from extrapyramidal side effects, a selective dopamine autoreceptor agonist with much lower affinity for postsynaptic dopamine D_2 receptors. A specifically claimed compound from a series of chroman-2-ylmethylamino derivatives.

SOURCE – American Home Products.

REFERENCES

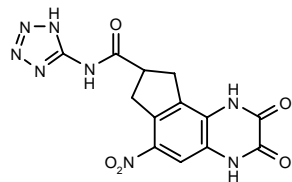
1. Mewshaw, R.E. (American Home Prods. Corp.) Chroman-2-ylmethylamino derivs. US 5756521.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

262922

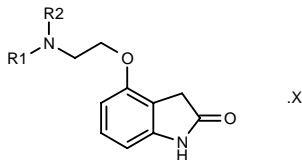
6-Nitro-2,3-dioxo-N-(1H-tetrazol-5-yl)-2,3,4,7,8,9-hexahydro-1H-cyclopenta[f]quinoxaline-8-carboxamide



C13-H10-N8-O5; Mol wt: 358.27

ACTION – Neuroprotective agent and anticonvulsant, a glutamate receptor antagonist with IC_{50} values of 0.07, 0.46 and 10 μ M, respectively, for AMPA and kainate receptors and the glycine site of the NMDA receptor. Compound is reported to be active in the maximal electroshock seizure assay and against AMPA-induced seizures in mice. A representative compound from a series of fused cycloalkyl quinoxalinediones, wherein the following are also included:

ACTION – Antipsychotic agent that acts as a dopamine autoreceptor agonist (IC_{50} = 0.41 nM against [3H]-quinpirole binding in rat striatal tissue), with reduced affinity for postsynaptic dopamine D_2 receptors (IC_{50} = 145 nM using [3H]-spiroperidol in rat limbic tissue). Also potentially useful for the treatment of Parkinson’s disease. Within this series of specifically claimed 4-aminoethoxy indolone derivatives, the following are also included:



Compound	R1	R2	X	Formula
264276	H	Me	fumarate	$C_{11}H_{14}N_2O_2 \cdot C_4H_4O_4$
264277	H	H		$C_{10}H_{12}N_2O_2$
264278	CH ₂ Ph	Me	fumarate H ₂ O	$C_{18}H_{20}N_2O_2 \cdot C_4H_4O_4 \cdot H_2O$
264279	3-Me-PhCH ₂	3-Me-PhCH ₂	fumarate	$C_{26}H_{28}N_2O_2 \cdot C_4H_4O_4$

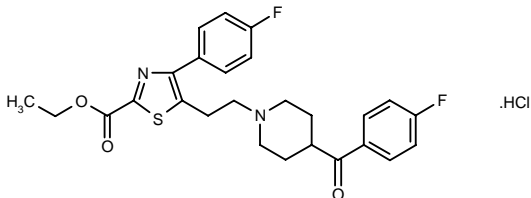
SOURCE – American Home Products.

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1. Mewshaw, R.E. (American Home Prods. Corp.) 4-Aminoethoxy indolone derivs. WO 9808819.

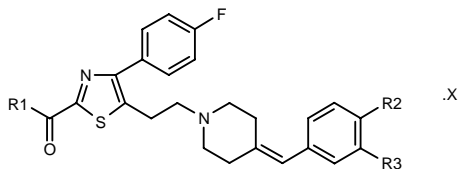
263889

5-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-4-(4-fluorophenyl)thiazole-2-carboxylic acid ethyl ester hydrochloride



C26-H26-F2-N2-O3-S.HCl; Mol wt: 521.02

ACTION – Agent for the treatment of disorders such as schizophrenia, cerebrovascular disorders and senile dementia, a potent and selective dopamine D_4 receptor antagonist (IC_{50} = 3.43 nM against [3H]-spiperone binding to human receptors expressed in CHO cells) with low potential for inducing extrapyramidal side effects due to its low affinity for dopamine D_2 receptors (IC_{50} > 1000 nM). Within this series of 2-carbonylthiazole derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
264710	NH ₂	F	H		$C_{24}H_{23}F_2N_3OS$
264711	OE _t	H	F	HCl	$C_{26}H_{26}F_2N_2O_2S \cdot HCl$
264713	OK	H	F		$C_{24}H_{21}F_2KN_2O_2S$
264714	NH ₂	H	H		$C_{24}H_{24}FN_3OS$

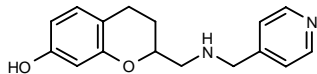
SOURCES – Nihon Nohyaku; Taisho.

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1. Nakazato, A. et al. (Taisho Pharm. Co., Ltd.; Nihon Nohyaku Co., Ltd.) 2-Carbonylthiazole derivs. and use of the same. WO 9812195.

264051

2-(4-Pyridylmethylaminomethyl)-3,4-dihydro-2H-1-benzopyran-7-ol



C16-H18-N2-O2; Mol wt: 270.33

ACTION – Antipsychotic agent reported to be free from extrapyramidal side effects, a selective dopamine autoreceptor agonist with much lower affinity for postsynaptic dopamine D_2 receptors. A specifically claimed compound from a series of chroman-2-ylmethylamino derivatives.

SOURCE – American Home Products.

REFERENCES

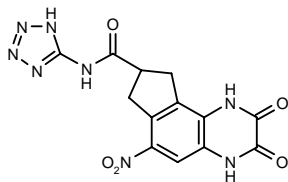
1. Mewshaw, R.E. (American Home Prods. Corp.) Chroman-2-ylmethylamino derivs. US 5756521.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

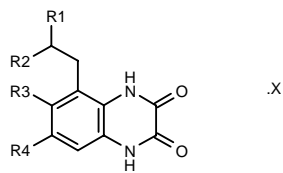
262922

6-Nitro-2,3-dioxo-N-(1H-tetrazol-5-yl)-2,3,4,7,8,9-hexahydro-1H-cyclopenta[f]quinoxaline-8-carboxamide



C13-H10-N8-O5; Mol wt: 358.27

ACTION – Neuroprotective agent and anticonvulsant, a glutamate receptor antagonist with IC_{50} values of 0.07, 0.46 and 10 μ M, respectively, for AMPA and kainate receptors and the glycine site of the NMDA receptor. Compound is reported to be active in the maximal electroshock seizure assay and against AMPA-induced seizures in mice. A representative compound from a series of fused cycloalkyl quinoxalinediones, wherein the following are also included:



Compound	R1	R2	R3	R4	X	Formula
263582	NHMe	-(CH2)2-	H	H	HCl	C ₁₃ H ₁₅ N ₃ O ₂ .HCl
263583	NHMe	-(CH2)2-	NO2			C ₁₃ H ₁₄ N ₄ O ₄
263584	OH	-(CH2)2-	Br			C ₁₂ H ₁₁ BrN ₂ O ₃
263585	NH2	-(CH2)2-	H			C ₁₂ H ₁₃ N ₃ O ₂
263587	1,3,4-thiadiazol-2-yl-NHCO	-CH2-	NO2			C ₁₄ H ₁₀ N ₆ O ₅ S
263588	2-thienyl-NHCO	-CH2-	NO2			C ₁₆ H ₁₂ N ₄ O ₅ S
263589	1,3,4-triazol-2-yl-NHCO	-CH2-	NO2			C ₁₄ H ₁₁ N ₇ O ₅

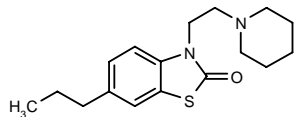
SOURCE – Warner-Lambert.

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1. Bigge, C.F. and Retz, D.M. (Warner-Lambert Co.) *Novel glutamate receptor antagonists: Fused cycloalkyl quinoxalinediones*. WO 9805651.

262985

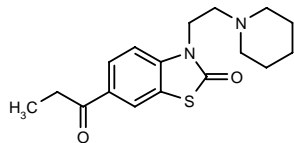
3-[2-(1-Piperidinyl)ethyl]-6-propylbenzothiazol-2(3H)-one



C17-H24-N2-O-S; Mol wt: 304.45

M.p. 147-9 °C.

ACTION – Anticonvulsant, a potent σ_1 -receptor ligand (K_i = 0.6 nM) with good selectivity over the σ_2 -receptor subtype (K_i = 18.1 nM) and little or no affinity for opioid, 5-HT₂, dopamine D₂ and muscarinic M₂ receptors. Compound was found to protect against maximal electroshock seizures with an ED₅₀ of 7.6 mg/kg i.p. in mice and an ED₅₀ of 18.6 mg/kg p.o. in rats, but it was ineffective against pentylenetetrazol-induced seizures at 100 mg/kg i.p. in mice. Neurotoxicity was determined by the rotarod test in mice, giving a median neurotoxic dose (TD₅₀) of 29.4 mg/kg i.p. (protective index [PI = TD₅₀/ED₅₀] = 3.9). Another anticonvulsant benzothiazolone is:



262986: C17-H22-N2-O2-S

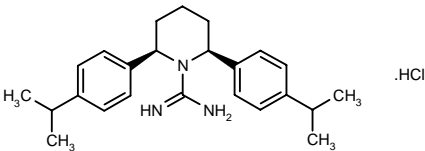
SOURCES – Univ. Bologna, Bologna (IT); Univ. Liège, Liège (BE); Univ. Louvain, Brussels (BE); Natl. Inst. Health, Bethesda, MD (US).

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1. Ucar, H. et al. *Synthesis and anticonvulsant activity of 2(3H)-benzoxazolone and 2(3H)-benzothiazolone derivatives*. J Med Chem 1998, 41(7): 1138.
2. Ucar, H. et al. *2(3H)-Benzoxazolone and 2(3H)-benzothiazolone derivatives: Novel potent and selective sigma1 receptor ligands*. Eur J Pharmacol 1997, 335(2-3): 267.

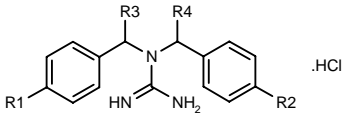
263242

cis-2,6-Bis(4-isopropylphenyl)piperidine-1-carboxamide hydrochloride



C24-H33-N3.HCl; Mol wt: 400.01

ACTION – Neuroprotective agent with anticonvulsant activity *in vivo* against audiogenic seizures in mice (69% inhibition at 10 mg/kg i.p.). Also potentially useful in the treatment of stroke, brain or spinal cord trauma, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Other specifically claimed imine-substituted heterocyclic compounds include the following:



Compound	R1=R2	R3,R4	Isomer	Formula
263557	Me	-(CH2)3-	cis	C ₂₀ H ₂₅ N ₃ .HCl
263558	Me	-(CH2)3-	trans	C ₂₀ H ₂₅ N ₃ .HCl
263559	H	-(CH2)2-	cis	C ₁₇ H ₁₉ N ₃ .HCl

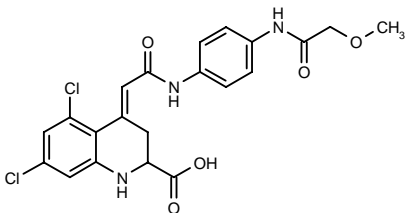
SOURCE – Cambridge NeuroScience.

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1. Durant, G.J. et al. (Cambridge NeuroScience, Inc.) *Pharmaceutically active cpds. and methods of use*. WO 9806401.

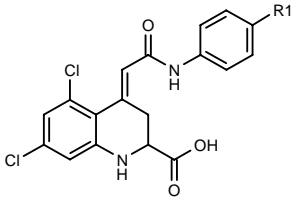
263296

(±)-(E)-5,7-Dichloro-4-[N-[4-(2-methoxyacetamido)-phenyl]carbamoylmethylene]-1,2,3,4-tetrahydroquinoline-2-carboxylic acid



C21-H19-Cl2-N3-O5; Mol wt: 464.30

ACTION – Agent for the treatment or prevention of neurotoxic damage and neurodegenerative disorders, a potent and selective antagonist at the strychnine-insensitive glycine binding site on the NMDA receptor ($pK_i = 8.2$) with little or no affinity for kainate and AMPA receptors. *In vivo*, compound produced 40% inhibition of NMDA-induced convulsions in mice at 0.1 mg/kg i.v. Other specifically claimed compounds from this series of tetrahydroquinoline derivatives include the following:



Compound	R1	Formula
263916	i-PrCONHCH2CONH	C ₂₄ H ₂₄ Cl ₂ N ₄ O ₅
263917	CH2CN	C ₂₀ H ₁₅ Cl ₂ N ₃ O ₃
263918	CH=CHCN	C ₂₁ H ₁₅ Cl ₂ N ₃ O ₃
263919	(E)-t-BuOCOCH=CH	C ₂₅ H ₂₄ Cl ₂ N ₂ O ₅
263920	(E)-CH=CHCONH2	C ₂₁ H ₁₇ Cl ₂ N ₃ O ₄
263921	i-PrCONHCH2CH2O	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₅
263922	4-morpholinyl-CH2CH2O	C ₂₄ H ₂₅ Cl ₂ N ₃ O ₅

SOURCE – Glaxo Wellcome.

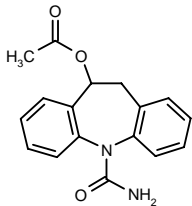
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263738

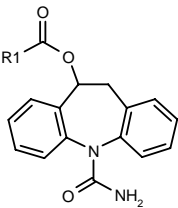
10-Acetoxy-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide

Acetic acid 5-carbamoyl-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10-yl ester



C17-H16-N2-O3; Mol wt: 296.33

ACTION – Agent for the treatment of epilepsy, trigeminal neuralgia, affective disorders and neurodegenerative or cerebral ischemic disorders, a derivative of oxcarbazepine proven to possess comparable or superior anticonvulsant activity in the maximal electroshock (MES) and metrazol tests in rats. Other specifically claimed oxcarbazepine derivatives include the following:



Compound	R1	Formula
263969	Ph	C ₂₂ H ₁₈ N ₂ O ₃
263970	4-MeO-Ph	C ₂₃ H ₂₀ N ₂ O ₄
263971	3-MeO-Ph	C ₂₃ H ₂₀ N ₂ O ₄
263972	2-MeO-Ph	C ₂₃ H ₂₀ N ₂ O ₄
263973	4-NO2-Ph	C ₂₂ H ₁₇ N ₃ O ₅

SOURCE – Portela.

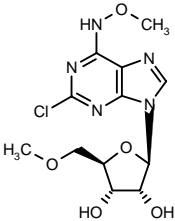
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1. Benes, J. (Portela & Ca., SA) *Substd. dihydrodibenzo[b,f]azepines, method of their preparation, their use in the treatment of some central nervous system disorders, and pharmaceutical compns. containing them*. US 5753646.

NNC-53-0055^{1,3,4}

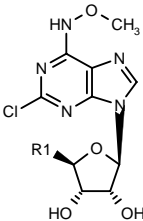
263719

2-Chloro-*N*⁶-methoxy-5'-*O*-methyladenosine



C12-H16-Cl-N5-O5; Mol wt: 345.74

ACTION – Potent and selective adenosine A₃ receptor agonist that modulates cytokine production, as demonstrated by potent inhibition of the production of tumor necrosis factor- α (TNF- α) in a rat whole blood assay. It also exerts potent effects in *in vivo* rodent models of epilepsy and cerebral ischemia. Potentially useful for the treatment of inflammatory and autoimmune conditions as well as CNS disorders. Other *N*-alkoxypurines include the following:



Compound	R1	Formula
NNC-21-0113 ^{1,13} [224227]	CH2Cl	C ₁₁ H ₁₃ Cl ₂ N ₅ O ₄
NNC-53-0002 ^{11,2,3} [261212]	CH2OAc	C ₁₃ H ₁₆ ClN ₅ O ₆
NNC-21-0238 ^{1,3} [263723]	vinyl	C ₁₂ H ₁₄ ClN ₅ O ₄
NNC-53-0082 ^{2,3} [263725]	3-isoxazolyl	C ₁₃ H ₁₃ ClN ₆ O ₅

SOURCE – Novo Nordisk.

REFERENCES

1. Lau, J. and Knutsen, L.J.S. (Novo Nordisk A/S) *Chemical cpds., their preparation and use*. EP 719275, US 5589467, WO 9507921.

2. Knutsen, L. et al. (Novo Nordisk A/S) *Novel N-alkoxyadenine derivs. acting as cytokine inhibitors*. WO 9801459.

3. Knutsen, L.J.S. et al. *New adenosine A1 and A3 selective N-alkoxypurines*. Drug Develop Res 1998, 43(1): Abst 96.

4. Spedding, M. and Williams, M. *Developments in purine and pyrimidine receptor-based therapeutics*. Drug Develop Res 1996, 39(3-4): 436.

*Identified compound **224227** (see **222404**) Drug Data Rep 1995, 17(8): 704.

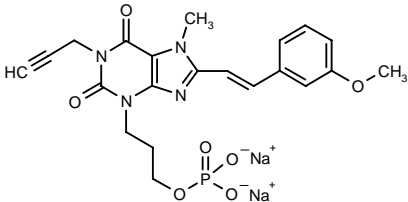
Identified compound **261212 Drug Data Rep 1998, 20(4): 324.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

MSX-3

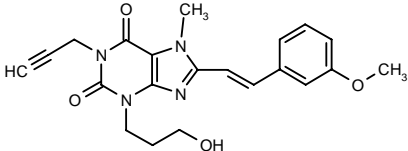
263727

Phosphoric acid 3-[8-[2(E)-(3-Methoxyphenyl)vinyl]-7-methyl-1-(2-propynyl)xanthin-3-yl]propyl monoester disodium salt



C21-H21-N4-Na2-O7-P; Mol wt: 518.37

ACTION – Highly water-soluble prodrug of the potent and selective adenosine A_{2A} receptor antagonist **MSX-2** that is hydrolyzed *in vivo* by phosphatases to yield the latter. Intrastratial application of the prodrug (1 ml/hemisphere of a 9 mg/ml solution) significantly reduced catalepsy in rats induced by raclopride or Sch-23390 (dopamine D₂ and D₁ receptor antagonist, respectively), whereas by itself it induced increases in motor activity; the onset of effect was rapid and lasted for at least 15 min. Potentially useful for the treatment of Parkinson's disease.



MSX-2 [263728]: C21-H22-N4-O4

SOURCES – Univ. Stuttgart (DE); Univ. Wuerzburg (DE).

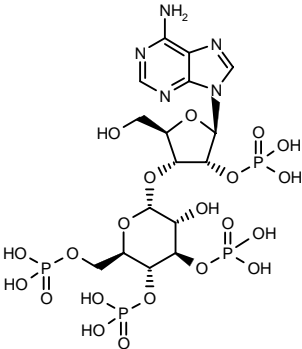
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1. Müller, C.E. et al. *Water-soluble prodrugs of potent A_{2A}-selective adenosine receptor antagonists*. Drug Dev Res 1998, 43(1): Abst 128A.

COGNITION-ENHANCING DRUGS

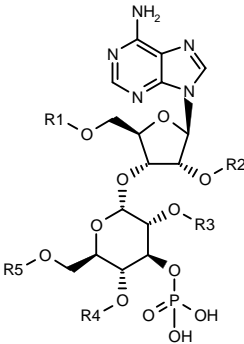
259199

2'-O-Phospho-3'-O-(3,4,6-tri-O-phospho-α-D-glucopyranosyl)adenosine



C16-H27-N5-O21-P4; Mol wt: 749.31

ACTION – Nootropic agent for the treatment of senile dementia and Alzheimer's disease, able to bind to IP₃ (inositol 1,4,5-triphosphate) and increase intracellular Ca²⁺ concentrations. Also claimed for use as an immuno-stimulant, antiulcer and antidiabetic agent. Within this series of polyphosphate derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
263530	PO3H2	PO3H2	PO3H2	PO3H2	PO3H2	C ₁₆ H ₂₉ N ₅ O ₂₇ P ₆
263531	H	H	H	PO3H2	PO3H2	C ₁₆ H ₂₆ N ₅ O ₁₈ P ₃
263532	PO3H2	H	H	PO3H2	PO3H2	C ₁₆ H ₂₇ N ₅ O ₂₁ P ₄
263533	PO3H2	H	H	PO3H2	H	C ₁₆ H ₂₆ N ₅ O ₁₈ P ₃
263534	H	PO3H2	H	H	H	C ₁₆ H ₂₅ N ₅ O ₁₅ P ₂

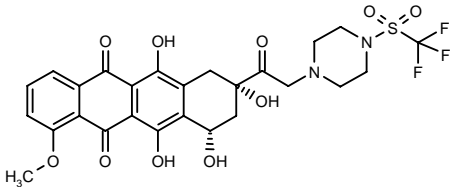
SOURCE – Sankyo.

REFERENCES

1. Hotoda, H. et al. (Sankyo Co., Ltd.) *Polyphosphate derivs*. JP 97316093.

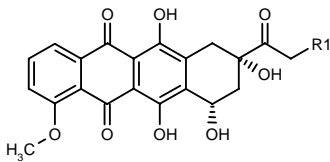
260172

14-[4-(Trifluoromethanesulfonyl)piperazin-1-yl]daunomycinone

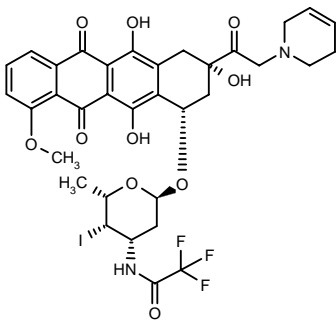


C26-H25-F3-N2-O10-S; Mol wt: 614.55

ACTION – Agent for the treatment or diagnosis of amyloidotic diseases such as Alzheimer’s disease, Down’s syndrome and spongiform encephalopathy, a fluorinated daunomycinone derivative found to bind to β-amyloid 25-35 fibrils and to have antifibrillogenic activity. Other specifically claimed compounds from this series of fluorinated anthracyclinone and anthracycline derivatives include the following:



Compound	R1	Formula
263188	4-(CF3CO)-1-Piz	C ₂₇ H ₂₅ F ₃ N ₂ O ₉
263189	4-(3-CF3-Ph)-1-Piz	C ₃₂ H ₂₆ F ₃ N ₂ O ₈
263190	3,5-(CF3)2-PhCH2N(Et)	C ₃₂ H ₂₇ F ₆ NO ₈
263191	N(CH2Ph)CH2CF3	C ₃₀ H ₂₆ F ₃ NO ₈



263192: C34-H34-F3-I-N2-O10

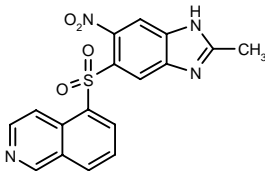
SOURCE – Pharmacia & Upjohn.

REFERENCES

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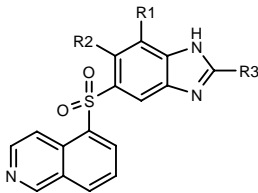
262921

5-(Isoquinolin-5-ylsulfonyl)-2-methyl-6-nitro-1*H*-benzimidazole

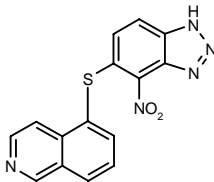


C17-H12-N4-O4-S; Mol wt: 368.37

ACTION – Neuroprotective agent, as demonstrated in human neuroblastoma SH-SY5Y cells by about 55% inhibition of colchicine-induced neuronal cell death at 30 μM and about 65% inhibition of 6-hydroxydopamine-induced neuronal cell death at 10 μM. Potentially useful for the treatment and prevention of neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea and amyotrophic lateral sclerosis, cerebral ischemic disorders and diabetic neuropathy. Other compounds from this series of isoquinoline derivatives include the following:



Compound	R1	R2	R3	Formula
263441	H	NO2	Et	C ₁₈ H ₁₄ N ₄ O ₄ S
263442	NO2	H	Et	C ₁₈ H ₁₄ N ₄ O ₄ S
263443	H	Cl	Pr	C ₁₉ H ₁₆ ClN ₃ O ₂ S
263445	H	NO2	cyclohexyl	C ₂₂ H ₂₀ N ₄ O ₄ S
263446	H	Br	Et	C ₁₈ H ₁₄ BrN ₃ O ₂ S
263447	H	Br	cyclohexyl	C ₂₂ H ₂₀ BrN ₃ O ₂ S



263444: C15-H9-N5-O2-S

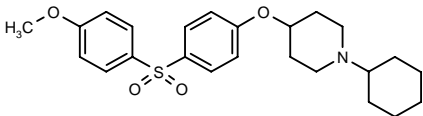
SOURCE – Snow Brand Milk Products.

REFERENCES

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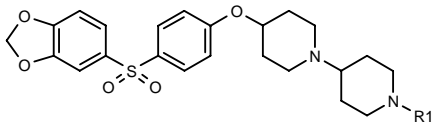
263250

1-Cyclohexyl-4-[4-(4-methoxyphenylsulfonyl)phenoxy]-piperidine



C24-H31-N-O4-S; Mol wt: 429.57

ACTION – Agent for the treatment of cognitive disorders such as Alzheimer’s disease, a muscarinic receptor antagonist reported to be selective for M₂ receptors. Within this series of specifically claimed 1,4-disubstituted piperidine derivatives, the following are also included:



Compound	R1	Formula
264514	2-Me-Ph	C ₃₀ H ₃₄ N ₂ O ₅ S
264515	i-BuOCO	C ₂₈ H ₃₆ N ₂ O ₇ S
264516	CO ₂ Ph	C ₃₀ H ₃₂ N ₂ O ₇ S
264517	SO ₂ Pr	C ₂₆ H ₃₄ N ₂ O ₇ S ₂
264518	SO ₂ Et	C ₂₅ H ₃₂ N ₂ O ₇ S ₂
264519	SO ₂ Bu	C ₂₇ H ₃₆ N ₂ O ₇ S ₂
264520	SO ₂ CH ₂ Ph	C ₃₀ H ₃₄ N ₂ O ₇ S ₂

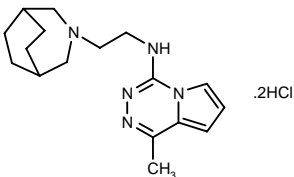
SOURCE – Schering Corp.

REFERENCES

1. Wang, Y. et al. (Schering Corp.) *Ether muscarinic antagonists*. WO 9806697.

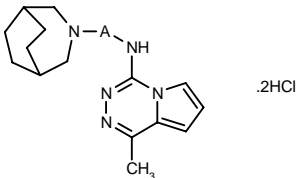
263485

N-[2-(3-Azabicyclo[3.2.2]non-3-yl)ethyl]-N-(1-methyl-pyrrolo[1,2-d][1,2,4]triazin-4-yl)amine dihydrochloride

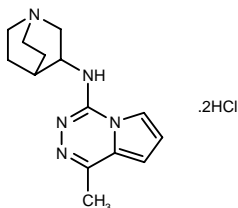


C17-H25-N5.2HCl; Mol wt: 336.89

ACTION – Agent for the treatment of cognitive disorders associated with decreased levels of acetylcholine such as Alzheimer’s disease, Parkinson’s disease or Down’s syndrome, with high affinity for central muscarinic receptors, particularly M₁ receptors. Compound inhibited [³H]-QNB binding to human M₁ receptors expressed in CHO cells with a K_i value of 4.45 μM and was shown to stimulate phosphoinositide hydrolysis in CHO cells expressing the M₁ receptor. Within this series of specifically claimed pyrrolo[1,2-d][1,2,4]triazines, the following are also included:



Compound	R1	Formula
263983	-(CH ₂) ₄ -	C ₁₉ H ₂₉ N ₅ ·2HCl
263984	-(CH ₂) ₃ -	C ₁₈ H ₂₇ N ₅ ·2HCl



263985: C14-H19-N5.2HCl

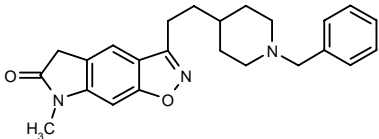
SOURCE – American Home Products.

REFERENCES

1. Sabb, A.L. et al. (American Home Prods. Corp.) *Pyrrolo[1,2-d][1,2,4]triazine derivs.* US 5750522.

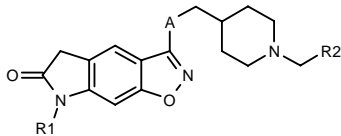
263486

3-[2-(1-Benzylpiperidin-4-yl)ethyl]-7-methyl-6,7-dihydro-5H-pyrrolo[3,2-f][1,2-b]benzisoxazol-6-one

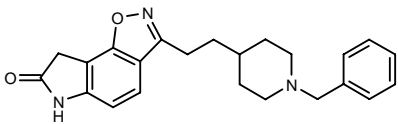


C24-H27-N3-O2; Mol wt: 389.50

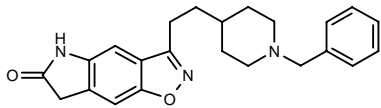
ACTION – Acetylcholinesterase inhibitor with potential in the treatment of dementia and Alzheimer’s disease from a series of benzisoxazole and benzisothiazole derivatives, wherein the following compounds are also specifically claimed:



Compound	R1	R2	A	Formula
263923	Et	Ph	-CH ₂ -	C ₂₅ H ₂₉ N ₃ O ₂
263924	H	5-Cl-2-thienyl	-CH ₂ -	C ₂₁ H ₂₂ ClN ₃ O ₂ S
263925	H	2-Me-4-thiazolyl	-CH ₂ -	C ₂₁ H ₂₄ N ₄ O ₂ S
263926	H	3-Br-Ph	-CH ₂ -	C ₂₃ H ₂₄ BrN ₃ O ₂
263927	H	4-Br-Ph	-CH ₂ -	C ₂₃ H ₂₄ BrN ₃ O ₂
263928	H	Ph	-(CH ₂) ₂ -	C ₂₄ H ₂₇ N ₃ O ₂



263929: C23-H25-N3-O2



263930: C23-H25-N3-O2

SOURCE – Pfizer.

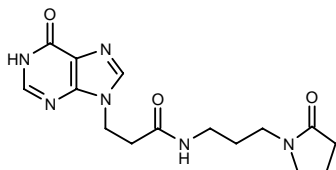
REFERENCES

1. Villalobos, A. et al. (Pfizer, Inc.) *Benzisoxazole and benzisothiazole derivs. acolinesterase inhibitors*. US 5750542.

AIT-034

193848

3-(6-Oxo-1,6-dihydro-9H-purin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl]propanamide



C15-H20-N6-O3; Mol wt: 332.36

ACTION – Cognition-enhancing agent, a derivative of hypoxanthine that inhibits somatostatin binding to brain membrane receptors, producing 68% displacement at 0.1 nM and 82% displacement at 10 μ M. Compound improved working memory in young adult mice on the T-maze win-shift paradigm at doses of 0.5-30 mg/kg i.p., and it also enhanced memory in aged mice. It does not enhance neurite outgrowth of PC12 cells, and it has no effect on locomotor activity, exploratory activity, anxiety or motor coordination in mice.

SOURCE – NeoTherapeutics.

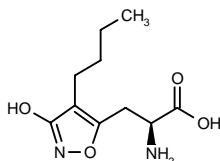
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1. Glasky, A.J. and Rathbone, M.P. *Carbon monoxide dependent guanylyl cyclase modifiers and methods of use*. US 5447939, WO 9603125.
2. Glasky, A.J. *Multi-functional pharmaceutical compsns. and methods of use*. WO 9114434.
3. Glasky, A. et al. *AIT-034 effects on somatostatin binding and working memory*. Soc Neurosci Abstr 1992, 18(Part 1): Abstr 362.11.
4. Glasky, A.J. et al. *AIT-034, a novel cognitive enhancing agent*. Soc Neurosci Abstr 1997, 23(Part 2): Abstr 717.5.
5. Glasky, A.J. et al. *Neuroprotective effects of hypoxanthine derivatives*. Drug Dev Res 1998, 43(1): Abstr 209.
6. *Company profile: NeoTherapeutics, Inc.* Prous Science Daily Essentials January 14, 1997.
7. *NeoTherapeutics' candidate compounds AIT-082 and AIT-034 presented at scientific meeting*. Prous Science Daily Essentials May 26, 1998.
8. *NeoTherapeutics' cognition enhancer in preclinical testing*. Prous Science Daily Essentials December 4, 1997.

(S)-Bu-HIBO

262030

2(S)-Amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid



C10-H16-N2-O4; Mol wt: 228.25

Hemihydrate, m.p. 227 °C, $[\alpha]_D^{25} +19.0^\circ$ (c 0.58, 1M HCl).

ACTION – AMPA receptor agonist (IC_{50} = 0.48 μ M against [3 H]-AMPA binding; EC_{50} = 17 μ M in electrophysiological experiments in the rat cortical wedge preparation) and inhibitor of $CaCl_2$ -dependent [3 H]-(S)-glutamic acid binding (IC_{50} = 0.64 μ M); it does not interact with kainic acid or NMDA receptor sites, and had little or no effect on

the function of the metabotropic (S)-glutamic acid receptors. After i.v. administration in mice, it displayed an ED_{50} of 44 μ mol/kg as a convulsant, being twice as potent as AMPA, indicating greater penetration through the blood-brain barrier. Potentially useful for the treatment of Alzheimer's disease and schizophrenia.

SOURCE – Lundbeck.

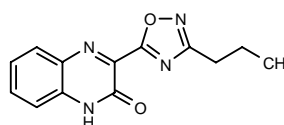
REFERENCES

1. Johansen, T.N. et al. *Excitatory amino acid receptor ligands: Resolution, absolute stereochemistry, and enantiopharmacology of 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid*. J Med Chem 1998, 41(6): 930.

SX-3507

262491

3-(3-Propyl-1,2,4-oxadiazol-5-yl)quinoxalin-2(1H)-one



C13-H12-N4-O2; Mol wt: 256.26

ACTION – A benzodiazepine (BZD) receptor inverse agonist potentially useful for the treatment of dementia.

SOURCE – Dainippon.

REFERENCES

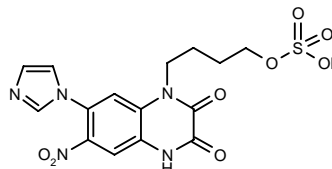
1. Masumoto, K. et al. *Synthesis and SARS of novel quinoxaline derivative having benzodiazepine (BZP) receptor inverse agonist action*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abstr 01(XD)10-1.

TREATMENT OF CEREBROVASCULAR DISEASES

260071

7-(1-Imidazolyl)-6-nitro-1-[4-(sulfooxy)butyl]quinoxaline-2,3(1H,4H)-dione

Sulfuric acid 4-[7-(1-imidazolyl)-6-nitro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-1-yl]butyl monoester



C15-H15-N5-O8-S; Mol wt: 425.37

ACTION – Neuronal injury inhibitor, a glutamate receptor antagonist with strong affinity for AMPA receptors (IC_{50} = 39 nM using [3 H]-AMPA as the ligand in rat fetal hippocampal nerve cells). Compound also exhibited potent inhibitory activity against kainate-induced neurotoxicity, with an IC_{50} of 0.16 μ M, and protected DBA/2 mice from audiogenic seizures (minimum effective dose [MED] = 3 mg/kg i.p.). A representative compound within a series of imidazole-substituted quinoxalinedione derivatives.

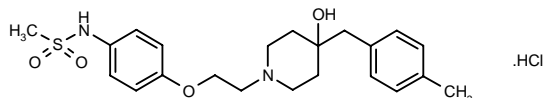
SOURCE – Yamanouchi.

REFERENCES

1. Sakamoto, S. et al. (Yamanouchi Pharm. Co., Ltd.) *Imidazole-substd. quinoxalinedione derivs.* WO 9746555.

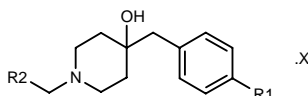
262085

N-[4-[2-[4-Hydroxy-4-(4-methylbenzyl)piperidin-1-yl]ethoxy]phenyl]methanesulfonamide hydrochloride



C22-H30-N2-O4-S.HCl; Mol wt: 455.01

ACTION – Neuronal injury inhibitor, an NMDA receptor antagonist with preference for the NR2B subunit, giving an IC₅₀ value of 0.030 μM against [³H]-Ro-25-6981 binding in rat brain membrane preparations; in electrophysiological studies, it gave 90% block of ion current at 0.1 μM in oocytes containing NR1C + NR2B subunits versus 29% block at 10 μM in oocytes containing NR1C + NR2A subunits. Other specifically claimed 4-hydroxy-piperidine derivatives include the following:



Compound	R1	R2	R3	Formula
262847	Me	4-OH-PhOCH2	fumarate	C ₂₁ H ₂₇ NO ₃ ·C ₄ H ₄ O ₄
262849	Me	4-OH-PhNHCO	HCl	C ₂₁ H ₂₆ N ₂ O ₃ ·HCl
262850	Me	4-OH-PhCH2CH(OH)	HCl	C ₂₂ H ₂₉ NO ₃ ·HCl
262851	Cl	4-OH-PhCH2CH(OH)	HCl	C ₂₁ H ₂₆ ClNO ₃ ·HCl
262852	Me	4-OH-PhCONHCH2	HCl	C ₂₂ H ₂₈ N ₂ O ₃ ·HCl

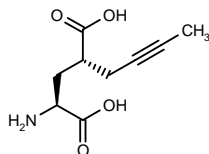
SOURCE – Roche.

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1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *4-Hydroxy-piperidine derivs.* EP 824098, JP 98067742.

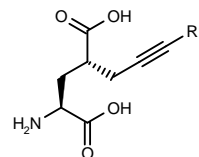
262099

(2*S*,4*R*)-2-Amino-4-(2-butylnyl)glutaric acid



C9-H13-N-O4; Mol wt: 199.21

ACTION – Agent for the treatment of CNS and neurodegenerative disorders such as stroke, Alzheimer's disease, cerebral ischemia, anxiety and depression that possesses affinity for and functional activity at the ionotropic glutamate receptor subtype GluR5. Within this series of alkylamino acid derivatives, the following are also included:



Compound	R1	Formula
262871	Et	C ₁₀ H ₁₅ NO ₄
262872	Pr	C ₁₁ H ₁₇ NO ₄
262873	H	C ₈ H ₁₁ NO ₄
262874	Ph	C ₁₄ H ₁₅ NO ₄

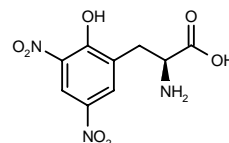
SOURCE – Lilly.

REFERENCES

1. Baker, S.R. et al. (Eli Lilly & Co., Ltd.; Lilly SA) *Alkylamino acid derivs. and their use as pharmaceutical cpds.* EP 826663, JP 98087585.

262971

2(*S*)-Amino-3-(2-hydroxy-3,5-dinitrophenyl)propionic acid



C9-H9-N3-O7; Mol wt: 271.19

Yellow crystals, 243-5 °C (decomp.).

ACTION – Agent for the treatment of neurodegenerative disorders and drug addiction, an AMPA receptor antagonist with an IC₅₀ of 13 μM and 5-fold selectivity over kainate receptors. In functional assays, compound inhibited AMPA-induced [³H]-norepinephrine release from mouse hippocampal slices with an IC₅₀ of 630 μM.

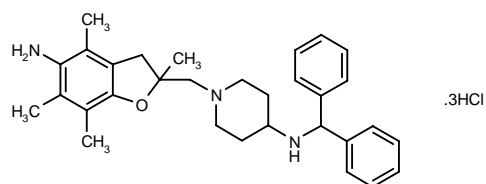
SOURCE – Ohio State Univ., Columbus, OH (US).

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1. Hill, R.A. et al. *Structure-activity studies for α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid receptors: Acidic hydroxyphenylalanines.* J Med Chem 1997, 40(20): 3182.
2. Sun, G. et al. *Design and synthesis of enantiomers of 3,5-dinitro-*o*-tyrosine: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) receptor antagonists.* J Med Chem 1998, 41(7): 1034.

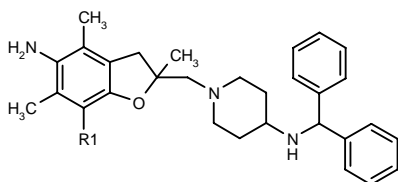
263360

N-[1-(5-Amino-2,4,6,7-tetramethyl-2,3-dihydro-benzofuran-2-ylmethyl)piperidin-4-yl]-*N*-(diphenylmethyl)amine trihydrochloride



C31-H39-N3-O.3HCl; Mol wt: 579.05

ACTION – Sodium channel modulator with high affinity for sodium channels, particularly for site 2, as demonstrated in a binding assay by an IC_{50} value of 0.16 μM against [3H]-batracotoxinin A20- α -benzoate binding using rat cerebral cortex membranes, and reported to possess a low toxic potential and a low risk for side effects. Potentially useful for the treatment of CNS disorders including ischemia, trauma, epilepsy, neurodegenerative disorders, vascular dementia, psychosis, depression, schizophrenia, trigeminal neuralgia, migraine and cerebral edema. It is also reported to possess excellent antioxidant and dopamine transporter-modulating activities and may therefore be useful for the treatment of cardiovascular disorders such as myocardial infarction, angina pectoris and atherosclerosis. Other specifically claimed compounds from this series of cyclic ether derivatives include the following:



Compound	R1	Isomer	Formula
264460	Me	(-)	C ₃₁ H ₃₉ N ₃ O
264461	Me	(+)	C ₃₁ H ₃₉ N ₃ O
264462	i-Pr		C ₃₃ H ₄₃ N ₃ O
264464	i-Pr	(-)	C ₃₃ H ₄₃ N ₃ O
264465	i-Pr	(+)	C ₃₃ H ₄₃ N ₃ O

SOURCE – Takeda.

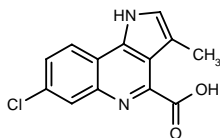
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1. Ohkawa, S. et al. (Takeda Chem. Ind., Ltd.) *Cyclic ether cpds. as sodium channel modulators*. WO 9808842.

FCE-27605

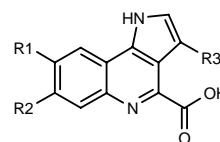
262923

7-Chloro-3-methyl-1*H*-pyrrolo[3,2-*c*]quinoline-4-carboxylic acid



C13-H9-Cl-N2-O2; Mol wt: 260.68

ACTION – Neuroprotective agent, a kynurenine 3-hydroxylase (kynurenine 3-monooxygenase) inhibitor (IC_{50} = 24 and 11 μM , respectively, in rat liver mitochondrial extracts and rat brain preparations). Claimed for the treatment or prevention of cerebral ischemia, hypoxia, Parkinson's disease, epilepsy, Huntington's chorea, Alzheimer's disease and other types of dementia, head or spinal cord injury, amyotrophic lateral sclerosis, glaucoma, retinopathy and infections and inflammation of the brain. Within this series of pyrrolo[3,2-*c*]quinolines, the following are also included:



Compound	R1	R2	R3	Formula
FCE-29370 [263184]	Cl	H	Me	C ₁₃ H ₉ ClN ₂ O ₂
FCE-29464 [263185]	H	Cl	Ph	C ₁₈ H ₁₁ ClN ₂ O ₂

SOURCE – Pharmacia & Upjohn.

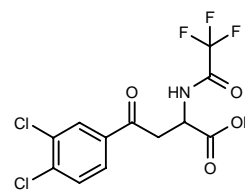
REFERENCES

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FCE-29256

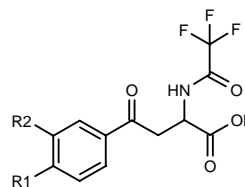
263794

4-(3,4-Dichlorophenyl)-4-oxo-2-(trifluoroacetamido)butyric acid



C12-H8-Cl2-F3-N-O4; Mol wt: 358.10

ACTION – Agent for the treatment and prevention of neurodegenerative diseases such as Huntington's chorea, Alzheimer's disease, AIDS-related dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma, retinopathy, infections and inflammation of the brain, an inhibitor of kynurenine 3-monooxygenase (kynurenine 3-hydroxylase; IC_{50} = 0.14 μM in rat brain preparations). Other compounds from this series of 2-amino-4-oxo-4-phenylbutyric acid derivatives include the following:



Compound	R1=R2	Isomer	Formula
FCE-29434 [264707]	Cl	S	C ₁₂ H ₈ Cl ₂ F ₃ NO ₄
FCE-29435 [264708]	F		C ₁₂ H ₈ F ₅ NO ₄

SOURCE – Pharmacia & Upjohn.

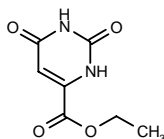
REFERENCES

1. Varasi, M. et al. (Pharmacia & Upjohn SpA) *N-Substd.-2-amino-4-phenyl-4-oxo-butyanoic acid derivs. with kynurenine-3-hydroxylase inhibitory activity* WO 9809938.

YM-39558**263529**

2,6-Dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ethyl ester

Orotic acid ethyl ester



C7-H8-N2-O4; Mol wt: 184.15

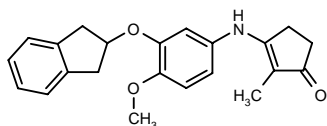
ACTION – Neuroprotective agent, an orotic acid prodrug that can cross the blood–brain barrier and provide higher levels of orotic acid in cerebrospinal fluid than orotic acid itself. Compound significantly protected hippocampal CA1 neurons in a gerbil model of transient forebrain ischemia, with a reduction in CA1 cell death scores from 3.0 to 1.4 at a dose of 100 mg/kg i.p. at 1, 4 and 8 h after reperfusion, whereas orotic acid at the same dose did not provide significant protection.

SOURCE – Yamanouchi.**REFERENCES**

1. Akiho, H. et al. *Neuroprotective effect of YM-39558, orotic acid ethylester, in gerbil forebrain ischemia*. Jpn J Pharmacol 1998, 76(4): 441.

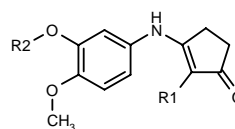
RESPIRATORY DRUGS**ASTHMA THERAPY****262818**

3-[3-(Indan-2-yloxy)-4-methoxyphenylamino]-2-methyl-2-cyclopenten-1-one

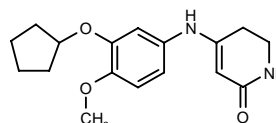


C22-H23-N-O3; Mol wt: 349.43

ACTION – Agent for the treatment of inflammatory, allergic and autoimmune disorders, an inhibitor of phosphodiesterase type IV (PDE IV; IC₅₀ = 0.14 μM against enzyme from rat neutrophils) with at least 10-fold selectivity relative to other PDE subtypes. *In vivo*, it inhibited antigen-induced bronchoconstriction in sensitized guinea pigs with an ED₅₀ value of 0.86 mg/kg i.v. Other related compounds include the following:



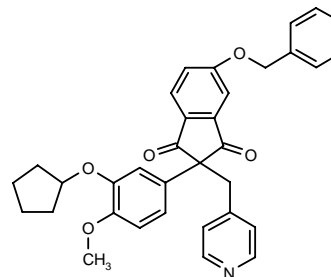
Compound	R1	R2	Formula
263095	Et	2-indanyl	C ₂₃ H ₂₅ NO ₃
263096	H	cyclopentyl	C ₁₇ H ₂₁ NO ₃
263097	H	exo-bicyclo[2.2.1]heptan-2-yl	C ₁₉ H ₂₃ NO ₃
263098	H	2-indanyl	C ₂₁ H ₂₁ NO ₃

**263099**: C17-H22-N2-O3**SOURCE** – Nikken Chem.**REFERENCES**

1. Ine, M. et al. (Nikken Chem. Co., Ltd.) *3-Anilino-2-cycloalkenone derivs*. JP 98072415.

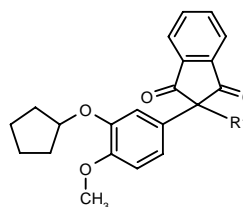
262905

6-Benzyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridylmethyl)indane-1,3-dione



C34-H31-N-O5; Mol wt: 533.62

ACTION – Agent for the treatment of inflammation, asthma or autoimmune diseases, an inhibitor of tumor necrosis factor (TNF) production and of type IV cAMP phosphodiesterase (PDE IV). Other specifically claimed substituted aromatic compounds include the following:



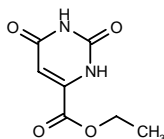
Compound	R1	Formula
263946	t-BuOCO(CH ₂) ₃	C ₂₉ H ₃₄ O ₆
263947	4-Pyr-CH ₂	C ₂₇ H ₂₉ NO ₄
263948	3,5-(Cl) ₂ -4-Pyr-CH ₂	C ₂₇ H ₂₃ Cl ₂ NO ₄
263949	4-(CO ₂ Me)-PhCH ₂	C ₃₀ H ₂₈ O ₆
263950	CH ₂ Ph	C ₂₈ H ₂₆ O ₄
263951	3-Pyr-CH ₂	C ₂₇ H ₂₅ NO ₄

YM-39558

263529

2,6-Dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ethyl ester

Orotic acid ethyl ester



C7-H8-N2-O4; Mol wt: 184.15

ACTION – Neuroprotective agent, an orotic acid prodrug that can cross the blood–brain barrier and provide higher levels of orotic acid in cerebrospinal fluid than orotic acid itself. Compound significantly protected hippocampal CA1 neurons in a gerbil model of transient forebrain ischemia, with a reduction in CA1 cell death scores from 3.0 to 1.4 at a dose of 100 mg/kg i.p. at 1, 4 and 8 h after reperfusion, whereas orotic acid at the same dose did not provide significant protection.

SOURCE – Yamanouchi.**REFERENCES**

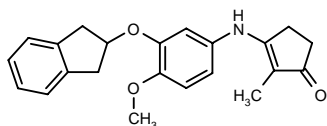
1. Akiho, H. et al. *Neuroprotective effect of YM-39558, orotic acid ethylester, in gerbil forebrain ischemia*. Jpn J Pharmacol 1998, 76(4): 441.

RESPIRATORY DRUGS

ASTHMA THERAPY

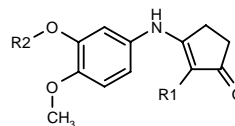
262818

3-[3-(Indan-2-yloxy)-4-methoxyphenylamino]-2-methyl-2-cyclopenten-1-one

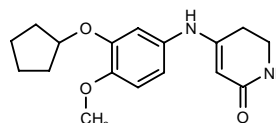


C22-H23-N-O3; Mol wt: 349.43

ACTION – Agent for the treatment of inflammatory, allergic and autoimmune disorders, an inhibitor of phosphodiesterase type IV (PDE IV; IC₅₀ = 0.14 μM against enzyme from rat neutrophils) with at least 10-fold selectivity relative to other PDE subtypes. *In vivo*, it inhibited antigen-induced bronchoconstriction in sensitized guinea pigs with an ED₅₀ value of 0.86 mg/kg i.v. Other related compounds include the following:



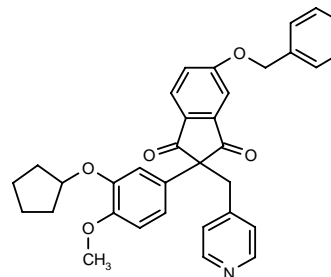
Compound	R1	R2	Formula
263095	Et	2-indanyl	C ₂₃ H ₂₅ NO ₃
263096	H	cyclopentyl	C ₁₇ H ₂₁ NO ₃
263097	H	exo-bicyclo[2.2.1]heptan-2-yl	C ₁₉ H ₂₃ NO ₃
263098	H	2-indanyl	C ₂₁ H ₂₁ NO ₃

**263099**: C17-H22-N2-O3**SOURCE** – Nikken Chem.**REFERENCES**

1. Ine, M. et al. (Nikken Chem. Co., Ltd.) *3-Anilino-2-cycloalkenone derivs*. JP 98072415.

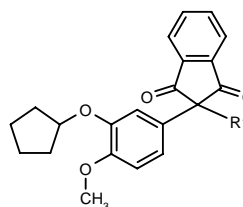
262905

6-Benzyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridylmethyl)indane-1,3-dione



C34-H31-N-O5; Mol wt: 533.62

ACTION – Agent for the treatment of inflammation, asthma or autoimmune diseases, an inhibitor of tumor necrosis factor (TNF) production and of type IV cAMP phosphodiesterase (PDE IV). Other specifically claimed substituted aromatic compounds include the following:



Compound	R1	Formula
263946	t-BuOCO(CH ₂) ₃	C ₂₉ H ₃₄ O ₆
263947	4-Pyr-CH ₂	C ₂₇ H ₂₉ NO ₄
263948	3,5-(Cl) ₂ -4-Pyr-CH ₂	C ₂₇ H ₂₃ Cl ₂ NO ₄
263949	4-(CO ₂ Me)-PhCH ₂	C ₃₀ H ₂₈ O ₆
263950	CH ₂ Ph	C ₂₈ H ₂₆ O ₄
263951	3-Pyr-CH ₂	C ₂₇ H ₂₅ NO ₄

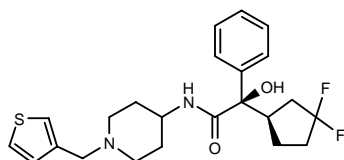
SOURCE – Rhône-Poulenc Rorer.

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1. He, W. et al. (Rhône-Poulenc Rorer Pharm., Inc.) *Substd. aromatic cpds.* WO 9805327.

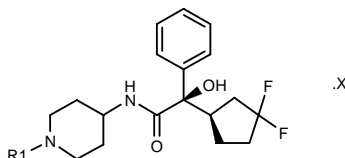
262919

2(*R*)-[3,3-Difluoro-1(*R*)-cyclopentyl]-2-hydroxy-2-phenyl-N-[1-(3-thienylmethyl)piperidin-4-yl]acetamide



C23-H28-F2-N2-O2-S; Mol wt: 434.54

ACTION – Potent and selective muscarinic M_3 receptor antagonist, as demonstrated in binding studies ($K_i = 3.2$ nM vs. 460 nM for M_2 receptors; M_2/M_3 ratio = 140) and in functional assays by potent inhibition of carbachol-induced contractions in isolated rat trachea (M_3 receptors; $K_B = 0.95$ nM) and a much weaker effect in rat right atrium (M_2 receptors; $K_B = 610$ nM; M_2/M_3 ratio = 640). *In vivo*, it inhibited acetylcholine-induced bronchoconstriction in rats upon i.v. ($ED_{50} = 0.032$ mg/kg) and p.o. administration ($ED_{50} = 0.22$ mg/kg). Other compounds from this series of fluorinated 1,4-disubstituted piperidine derivatives include the following:



Compound	R1	X	Formula
263438	CH ₂ CH ₂ CH=C(Me) ₂		C ₂₄ H ₃₄ F ₂ N ₂ O ₂
263439	6-NH ₂ -2-Pyr-CH ₂	2HCl	C ₂₄ H ₃₀ F ₂ N ₄ O ₂ ·2HCl
263440	3-MeO-4-NH ₂ -PhCH ₂		C ₂₆ H ₃₃ F ₂ N ₃ O ₃

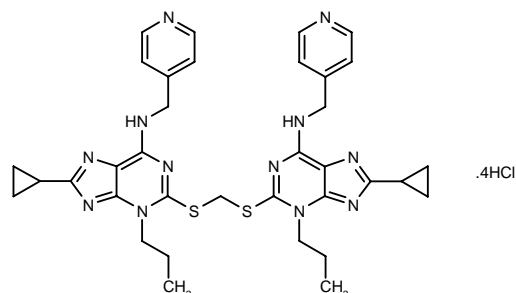
SOURCE – Banyu.

REFERENCES

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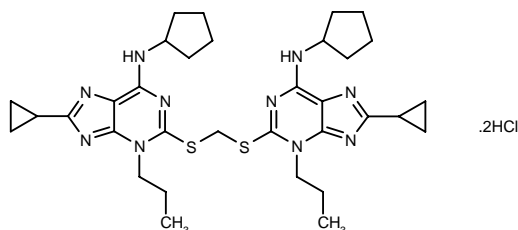
262931

2,2'-Methylenebis(thio)bis[8-cyclopropyl-3-propyl-6-(4-pyridylmethylamino)-3*H*-purine] tetrahydrochloride



C35-H40-N12-S2.4HCl; Mol wt: 838.75

ACTION – Agent for the treatment of inflammation, allergies and atopic diseases such as asthma and rhinitis, an inhibitor of phosphodiesterase type IV (PDE IV) with improved selectivity with regard to other PDE isozymes; in particular, title compound exhibited an IC_{50} of 0.029 μ M against PDE IV (bovine tracheal smooth muscle), an IC_{50} of 135.94 μ M against PDE III (human platelets) and an IC_{50} of 19.0 μ M against PDE V (human platelets), compared to respective IC_{50} values for rolipram of 3.7, 620 and 500 μ M. Another specifically claimed compound is:



263078: C33-H46-N10-S2.2HCl

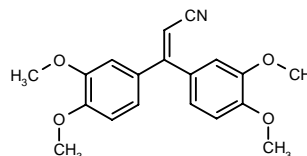
SOURCE – Euroceltique.

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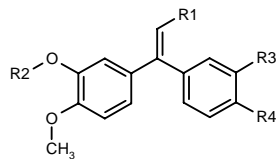
263247

3,3-Bis(3,4-dimethoxyphenyl)-2-propenenitrile



C19-H19-N-O4; Mol wt: 325.36

ACTION – Agent for the treatment of asthma, endotoxic shock, retrovirus replication, inflammatory conditions and cachexia that acts by inhibiting tumor necrosis factor- α (TNF- α) production, NF- κ B activation and/or phosphodiesterase (particularly PDE III and IV) activity. A compound within a wide series of specifically claimed cyano and carboxy derivatives of substituted styrenes, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
264529	CN	Et	OEt	OMe	C ₂₁ H ₂₃ NO ₄
264530	CO ₂ Me	Et	OEt	OMe	C ₂₂ H ₂₆ O ₆
264531	CO ₂ Me	Et	H	H	C ₁₉ H ₂₀ O ₄
264532	CN	Pr	H	H	C ₁₉ H ₁₉ NO ₂
264533	CN	Et	H	H	C ₁₈ H ₁₇ NO ₂
264534	CN	cyclopentyl	cyclopentyl-O	OMe	C ₂₇ H ₃₁ NO ₄
264535	CO ₂ Me	cyclopentyl	H	H	C ₂₂ H ₂₄ O ₄

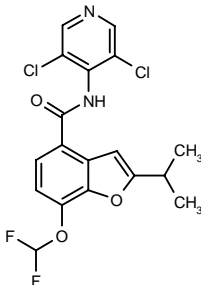
SOURCE – Celgene.

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1. Muller, G.W. and Shire, M. (Celgene Corp.) *Novel immunotherapeutic agents and their use in the reduction of cytokine levels.* WO 9806692.

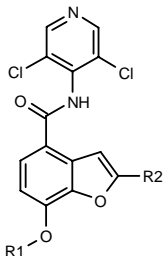
263302

N-(3,5-Dichloro-4-pyridyl)-7-(difluoromethoxy)-2-isopropylbenzofuran-4-carboxamide



C18-H14-Cl2-F2-N2-O3; Mol wt: 415.22

ACTION – Bronchodilating and antiinflammatory agent, an inhibitor of cyclic AMP phosphodiesterase, particularly PDE IV (–log IC₅₀ = 9.72), reported to possess low toxicity and high bioavailability. Claimed for use in the treatment of respiratory disorders. Within this series of benzofuran-4-carboxamides, the following are also included:



Compound	R1	R2	Formula
264005	Me	Me	C ₁₈ H ₁₂ Cl ₂ N ₂ O ₃
264006	Me	i-Pr	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃
264007	Et	i-Pr	C ₁₉ H ₁₈ Cl ₂ N ₂ O ₃
264008	Me	cyclopentyl	C ₂₀ H ₁₈ Cl ₂ N ₂ O ₃

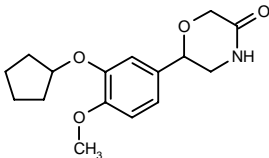
SOURCE – Byk Gulden.

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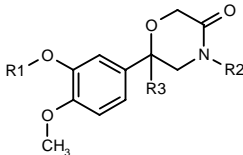
263350

2-(3-Cyclopentyloxy-4-methoxyphenyl)morpholin-5-one



C16-H21-N-O4; Mol wt: 291.35

ACTION – Bronchodilating and antiinflammatory agent that exerts its action through selective inhibition of phosphodiesterase type IV (PDE IV; IC₅₀ = 1.5 μM against enzyme isolated from rat neutrophils). It was active in inhibiting the release of superoxide anion in human neutrophils stimulated by Ca²⁺ ionophore A23187 (IC₅₀ = 5.8 μM), and it protected against bronchoconstriction elicited by ovalbumin in sensitized guinea pigs (ED₅₀ = 0.48 mg/kg i.v.). No deaths were observed in mice after 30 mg/kg i.p. Within this series of 2-phenylmorpholin-5-one derivatives, the following are also included:



Compound	R1	R2	R3	Formula
264149	Bu	H	H	C ₁₅ H ₂₁ NO ₄
264150	cyclopropyl-CH ₂	H	H	C ₁₅ H ₁₉ NO ₄
264151	Me	H	Me	C ₁₃ H ₁₇ NO ₄
264152	cyclopentyl	4-Br-PhCH ₂	H	C ₂₃ H ₂₆ BrNO ₄
264153	cyclopentyl	Me	H	C ₁₇ H ₂₃ NO ₄
264154	cyclopentyl-CH ₂	H	H	C ₁₇ H ₂₃ NO ₄

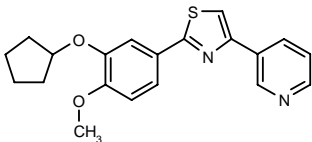
SOURCE – Nikken Chem.

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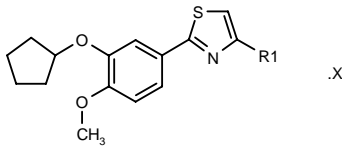
263352

2-(3-Cyclopentyloxy-4-methoxyphenyl)-4-(3-pyridyl)-thiazole



C20-H20-N2-O2-S; Mol wt: 352.45

ACTION – Selective inhibitor of phosphodiesterase type IV (PDE IV; $-\log IC_{50} = 7.82$) with potential in the treatment of asthma and other respiratory tract disorders. Within this series of thiazole derivatives, the following are also included:



Compound	R1	X	Formula
264545	Ph		$C_{21}H_{21}NO_2S$
264546	3-(CO ₂ Et)-Ph	HCl	$C_{24}H_{25}NO_4 \cdot HCl$
264547	4-CO ₂ H-Ph		$C_{22}H_{21}NO_4S$
264548	2-Pyr	HCl	$C_{20}H_{20}N_2O_2S \cdot HCl$
264549	4-Pyr	HCl	$C_{20}H_{20}N_2O_2S \cdot HCl$

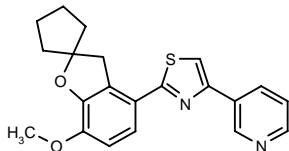
SOURCE – Byk Gulden.

REFERENCES

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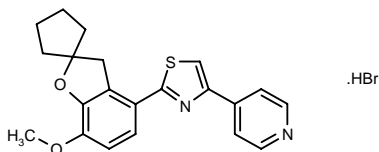
263359

3-[2-(7-Methoxyspiro[benzofuran-2(3*H*),1-cyclopentan]-4-yl)thiazol-4-yl]pyridine



C₂₁-H₂₀-N₂-O₂-S; Mol wt: 364.46

ACTION – A selective inhibitor of phosphodiesterase type IV (PDE IV; $-\log IC_{50} = 7.75$), with potential in the treatment of respiratory disorders such as asthma. Another compound from this series of thiazole derivatives is:



264445: C₂₁-H₂₀-N₂-O₂-S.HBr

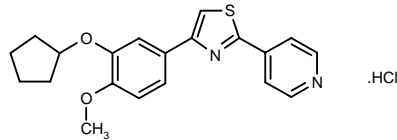
SOURCE – Byk Gulden.

REFERENCES

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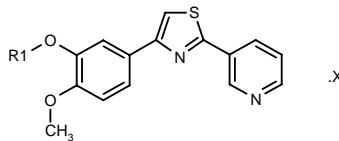
263362

4-[4-(3-Cyclopentyloxy-4-methoxyphenyl)thiazol-2-yl]pyridine hydrochloride



C₂₀-H₂₀-N₂-O₂-S.HCl; Mol wt: 388.91

ACTION – Bronchodilating agent, a selective inhibitor of phosphodiesterase type IV (PDE IV; $-\log IC_{50} = 8.06$). Other representative compounds within this series of thiazole derivatives include the following:



Compound	R1	X	Formula
264289	cyclopentyl	HCl	$C_{20}H_{20}N_2O_2S \cdot HCl$
264290	2-indanyl		$C_{24}H_{20}N_2O_2S$

SOURCE – Byk Gulden.

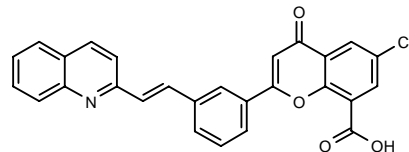
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VUF-5087

263501

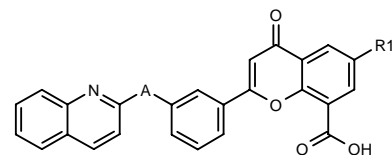
6-Chloro-4-oxo-2-[3-[2(*E*)-(2-quinolyl)vinyl]phenyl]-4*H*-1-benzopyran-8-carboxylic acid



C₂₇-H₁₆-Cl-N-O₄; Mol wt: 453.88

M.p. > 300 °C.

ACTION – Potential antiasthmatic agent, a CysLT₁ (LTD₄) receptor antagonist ($K_D = 11 \pm 3$ nM for inhibition of [³H]-LTD₄ binding in guinea pig lung membranes). *In vitro* it inhibited LTD₄-induced guinea pig ileum contractions with an IC_{50} of 15 nM. Other compounds from this series of carboxyflavones include the following:



Compound	R1	A	Formula
VUF-5017 [249908]	H	(<i>E</i>)-CH=CH-	$C_{27}H_{17}NO_4$
263503	Me	(<i>E</i>)-CH=CH-	$C_{28}H_{19}NO_4$
263504	Br	-CH ₂ O-	$C_{26}H_{16}BrNO_5$

SOURCES – Kowa; Vrije Univ., Amsterdam (NL).

REFERENCES

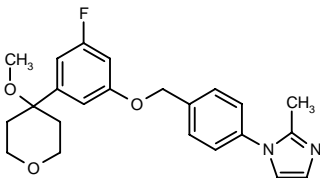
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3. Zwaagstra, M.E. et al. *Synthesis of carboxylated chalcones and flavones as potent Cys-LT1 receptor antagonists and the development of a 3D antagonist model*. 14th Int Symp Med Chem (Sept 8-12, Maastricht) 1996, Abst P-2.42.

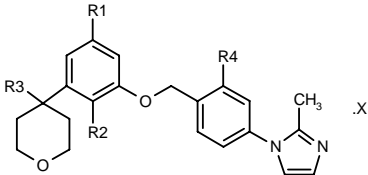
263744

4-[3-Fluoro-5-[4-(2-methylimidazol-1-yl)benzyloxy]-phenyl]-4-methoxytetrahydropyran



C23-H25-F-N2-O3; Mol wt: 396.46

ACTION – Agent for the treatment of bronchial asthma, skin disorders and arthritis, an inhibitor of 5-lipoxygenase. Other specifically claimed imidazole derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
263933	H	H	OMe	F		C ₂₃ H ₂₅ FN ₂ O ₃
263934	H	H	OMe	H		C ₂₃ H ₂₆ N ₂ O ₃
263935	F	H	SMe	H		C ₂₃ H ₂₅ FN ₂ O ₂ S
263936	F	F	OMe	H		C ₂₃ H ₂₄ F ₂ N ₂ O ₃
263938	F	H	OMe	H	HCl	C ₂₃ H ₂₅ FN ₂ O ₃ .HCl

SOURCE – Pfizer.

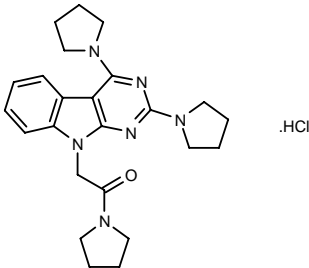
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1. Stevens, R.W. et al. (Pfizer, Inc.) *Imidazole lipoxygenase inhibitors*. US 5753682, WO 9429299.

PNU-142731A

263136

9-[2-Oxo-2-(pyrrolidin-1-yl)ethyl]-2,4-bis(pyrrolidin-1-yl)-9H-pyrimido[4,5-*b*]indole monohydrochloride



C24-H30-N6-O.HCl; Mol wt: 455.00

ACTION – Antiasthmatic agent, a nonglucocorticoid inhibitor of antigen-induced eosinophilic lung inflammation. In sensitized rats and mice, compound inhibited aerosol ovalbumin (OA)-induced eosinophilia in the bronchoalveolar lavage (BAL) and the associated histopathological changes; it also prevented OA-induced changes in microvascular permeability and mucosal edema. It appears to act by suppressing the mediators responsible for eosinophil recruitment, rather than via direct effects on eosinophils.

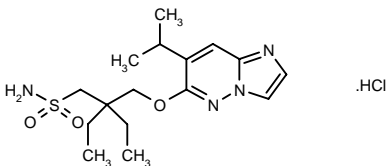
SOURCE – Pharmacia & Upjohn.

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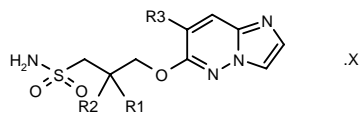
257473

2,2-Diethyl-3-(7-isopropylimidazo[1,2-*b*]pyridazin-6-yloxy)propanesulfonamide hydrochloride



C16-H26-N4-O3-S.HCl; Mol wt: 390.93

ACTION – Antiasthmatic and antiallergic agent with PAF-antagonist and eosinophil chemotaxis-inhibitory activity, as demonstrated by 79% inhibition of PAF-induced bronchoconstriction in guinea pigs at 1 mg/kg p.o. and 55% inhibition of LTB₄-induced guinea pig eosinophil chemotaxis at 10 μM. Within this series of imidazopyridazine derivatives, the following are also included:



Compound	R1=R2	R3	X	Formula
262990	Me	i-Pr		C ₁₄ H ₂₂ N ₄ O ₃ S
262991	Me	t-Bu		C ₁₅ H ₂₄ N ₄ O ₃ S
262992	Et	t-Bu		C ₁₇ H ₂₈ N ₄ O ₃ S
262993	Et	t-Bu	HCl	C ₁₇ H ₂₈ N ₄ O ₃ S.HCl

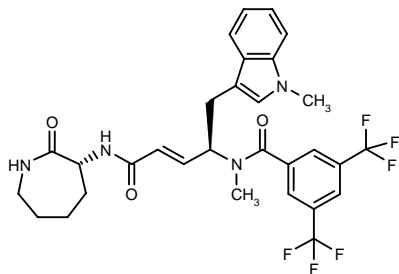
SOURCE – Takeda.

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1. Kawano, Y. and Ashida, Y. (Takeda Chem. Ind., Ltd.) *Imidazopyridazine derivs., preparation method thereof, intermediate and pharmaceutical compsns. containing them.* JP 97263586.

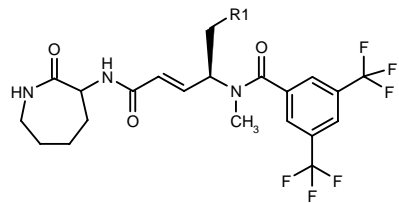
263290

4(R)-[N-Methyl-3,5-bis(trifluoromethyl)benzamido]-5-(1-methylindol-3-yl)-N-[2-oxoperhydroazepin-3(R)-yl]-2-pentenamide



C30-H30-F6-N4-O3; Mol wt: 608.58

ACTION – Neurokinin NK₁ and NK₂ receptor antagonist for the treatment of substance P- and neurokinin A-mediated disorders such as asthma and pain. Within this series of acylaminoalkenylene-amide derivatives, the following are also specifically claimed:



Compound	R1	Isomer	Formula
264025	1-Me-3-indolyl	S	C ₃₀ H ₃₀ F ₆ N ₄ O ₃
264026	4-Cl-Ph	R	C ₂₇ H ₂₆ ClF ₆ N ₃ O ₃
264027	3,4-(Cl)2-Ph	R	C ₂₇ H ₂₅ Cl ₂ F ₆ N ₃ O ₃

SOURCE – Novartis.

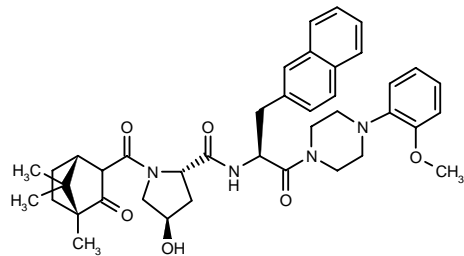
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1. Gerspacher, M. et al. (Novartis AG) *Acylaminoalkenylene-amide derivs. as NK1 and NK2 antagonists.* WO 9807694.

BIIC-1996*

231294

1-(2-Methoxyphenyl)-4-[1-[(1*R*,4*R*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-ylcarbonyl]-4(*R*)-hydroxy-L-prolyl-L-(2-naphthyl)alanyl]piperazine



C40-H48-N4-O6; Mol wt: 680.84

ACTION – Dual selective tachykinin NK₁/NK₂ receptor antagonist (K_i = 2 and 11 nM, respectively, using human receptors) potentially useful for the treatment of inflammatory airways diseases characterized by mucus hypersecretion, cough and bronchoconstriction. *In vivo*, the compound dose-dependently inhibited the blood pressure decrease induced by the selective NK₁ agonist [β-Ala⁴,Sar⁹,Met(O₂)¹¹]-SP(4-11) in anesthetized guinea pigs, with an ED₅₀ of 0.2 mg/kg i.v. and 4 mg/kg p.o., as well as the bronchoconstriction induced by the selective NK₂ agonist [β-Ala⁸]-NKA(4-10), with an ED₅₀ of 0.5 mg/kg i.v. It also inhibited NK₁-induced mucus secretion in isolated ferret trachea (IC₅₀ = 50 nM), citric acid-induced cough in guinea pigs (ED₅₀ = 0.2 mg/kg i.v.) and cigarette smoke-induced bronchial edema in guinea pigs (ED₅₀ = 0.5 mg/kg i.v.).

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Böck, G. et al. (Boehringer Ingelheim KG) *Pharmaceutical compsns. in form of liposomes.* DE 19623950.

2. Schnorrenberg, G. et al. (Boehringer Ingelheim KG) *Neurokine (tachykinine) antagonists.* DE 4445939, EP 804463, JP 97512806, US 5700827, US 5712273, WO 9530687.

3. Jung, B. et al. *Anti-inflammatory and bronchodilatory activity of a novel dual NK1/NK2 antagonist.* Amer J Respir Crit Care Med 1998, 157(3): A798.

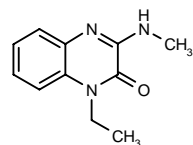
*Identified compound 231294 Drug Data Rep 1996, 18(5): 420.

L-0066*

244578

241751 (as hydrochloride)

1-Ethyl-3-(methylamino)quinoxalin-2(1*H*)-one



C11-H13-N3-O; Mol wt: 203.24

ACTION – Antiasthmatic agent that potently inhibits airways inflammation. In a model of lipopolysaccharide (LPS)-induced airways inflammation, administration 15 min prior to challenge with LPS decreased the number of neutrophils (ID_{50} = 19 mg/kg i.p.) and tumor necrosis factor (TNF- α) levels in the bronchoalveolar lavage fluid (BALF); when administered 5 min after LPS, it also decreased the number of neutrophils (ID_{50} = 11 mg/kg i.p.), but it did not affect TNF- α levels. In actively sensitized rats, it reduced allergen-induced eosinophilia and neutrophilia in BALF both acutely (i.p.) and chronically (p.o.).

SOURCE – Pierre Fabre.

REFERENCES

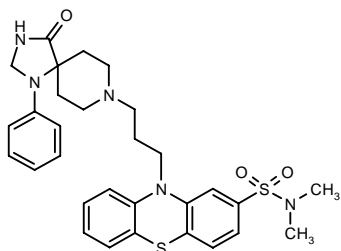
1. Bigg, D. et al. (Pierre Fabre Medicament) *1,2-Dihydro-2-oxo-3-amino quinoxaline derivs., preparation thereof and application in therapy*. EP 663903, FR 2696456, JP 96501793, US 5633255, WO 9407870.
2. Patoiseau, J.-F. et al. (Pierre Fabre Medicament) *Novel derivs. of ethyl-1 dihydro-1,2 oxo-2 methylamino-3 quinoxaline, utilization as drugs, and pharmaceutical compsns. containing them*. EP 812316, FR 2731221, WO 9626928.
3. Campbell, A.M. et al. *Effect of L0066, a novel compound with anti-PDE4 activity on mediator release from human nasal polyp cells*. J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 1026.
4. Kips, J.C. et al. *The effect of chronic treatment with L0066 on allergen induced airway inflammation in the rat*. Amer J Respir Crit Care Med 1998, 157(3): A824.
5. Lebel, B. et al. *Effect of 2 novel compounds on mediator release from human nasal polyp cells*. J Allergy Clin Immunol 1997, 99(1, Part 2): Abst 1479.
6. Tarayre, J.P. et al. *Comparative study of L0066 and anti-asthmatic drugs on late allergic bronchial inflammation in brown Norway rats*. Amer J Respir Crit Care Med 1998, 157(3): A824.
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*Identified compound **241751** Drug Data Rep 1997, 19(1): 34.

RP-23618

263170

N,N-Dimethyl-10-[3-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)propyl]-10*H*-phenothiazine-2-sulfonamide



C30-H35-N5-O3-S2; Mol wt: 577.76

ACTION – Specific, noncompetitive antagonist of the proinflammatory chemokine RANTES (Regulated on Activation Normal T-cell Expressed and Secreted), giving an IC_{50} value of 3 μ M for displacement of [125 I]-RANTES in THP-1 cell membranes; it did not inhibit [125 I]-MCP-1 binding at up to 30 μ M. RP-23618 concentration-dependently inhibited RANTES-induced THP-1 cell chemotaxis, but not that induced by MCP-1.

Increased RANTES expression has been detected in inflammatory disorders including asthma, arthritis and atherosclerosis.

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

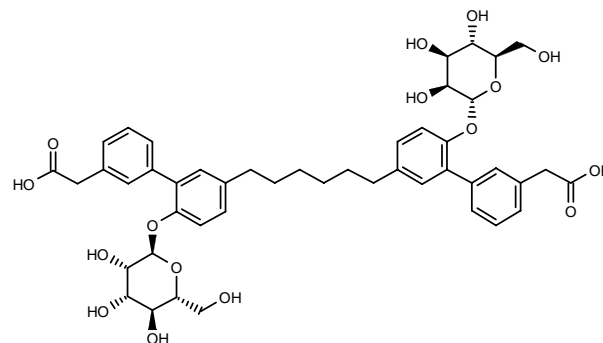
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TBC-1269*

247672

3,3'-(Hexane-1,6-diyl)bis[6-(α -D-mannopyranosyloxy)-3,1-phenylene]bis(phenylacetic acid)

3',3'''-(1,6-Hexanediyl)bis[6'-(α -D-mannopyranosyloxy)-[1,1'-biphenyl]-3-acetic acid]



C46-H54-O16; Mol wt: 862.92

White solid, m.p. 115-7 °C.

ACTION – Small-molecule sialyl Lewis X (sLe^x) mimetic that inhibits E-, P- and L-selectin-mediated cellular adhesion more potently than sLe^x; inhibiting the binding of sLe^x-expressing HL-60 cells to human E-, P- and L-selectin-IgG fusion proteins with respective IC_{50} values of 0.5, 0.07 and 0.56 mM (vs. 3.3, 3.4 and 3.5 mM, respectively, for sLe^x). In house dust mite-allergic rabbits with allergen-induced airways obstruction, TBC-1269 at 10 mg/rabbit given by aerosol 30 min prior to allergen challenge significantly improved both early- and late-phase bronchial hyperresponsiveness and airways obstruction, and inhibited lung eosinophilia. It also provided significant cardioprotection in dogs with ischemia-reperfusion injury at doses of 5-35 mg/kg i.v. Compound is in phase II trials for the treatment of asthma.

SOURCES – Texas Biotechnology; licensed to LG Chem.

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4. Kogan, T.P. et al. *Novel synthetic inhibitors of selectin-mediated cell adhesion: Synthesis of 1,6-bis[3-(3-carboxymethylphenyl)-4-(2- α -D-mannopyranosyloxy)phenyl]-hexane (TBC1269)*. J Med Chem 1998, 41(7): 1099.
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6. *IND filing anticipated for TBC-1269*. Prous Science Daily Essentials May 24, 1996.

7. *TBC-1269 enters phase II for treatment and prevention of asthma.* Prous Science Daily Essentials October 24, 1997.

8. *TBC cell adhesion inhibitor enters clinic.* Prous Science Daily Essentials January 22, 1997.

9. *Texas Biotechnology: Q3 1997 highlights.* Prous Science Daily Essentials November 14, 1997.

10. *Texas Biotechnology: Q4 1997 highlights.* Prous Science Daily Essentials March 2, 1998.

11. *Texas Biotechnology announces initiation of phase I clinical trial for TBC 1269 to treat asthma.* Texas Biotechnology, Corp. Press Release 1997, January 21.

12. *Texas Biotechnology announces strategic alliance with LG Chem - LG Chem to market two TBC therapeutics in Asia, excluding Japan.* Texas Biotechnology, Corp. Press Release 1996, October 10.

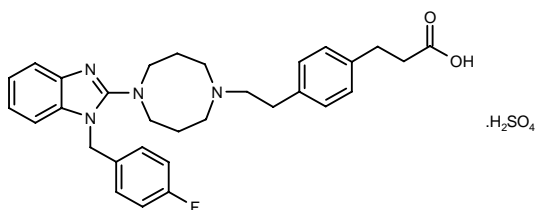
13. *Texas Biotechnology raises \$13.9 million in private financing.* Texas Biotechnology Corp. Press Release 1996, February 14.

*Identified compound **247672** Drug Data Rep 1997, 19(5): 414.

KAA-276

263124

3-[4-[2-[5-[1-(4-Fluorobenzyl)benzimidazol-2-yl]perhydro-1,5-diazocin-1-yl]ethyl]phenyl]propanoic acid sulfate



C31-H35-F-N4-O2.H2-S-O4; Mol wt: 612.71

ACTION – Potent and selective, nonsedating histamine H_1 receptor antagonist ($IC_{50} = 0.66$ nM for displacement of [3H]-mepyramine binding in guinea pig cerebellar membranes) with no significant affinity ($IC_{50} > 10,000$ nM) for α_1 -, α_2 -, β_1 - and β_2 -adrenoceptors, 5-HT $_1$ and 5-HT $_2$, histamine H_2 , nicotinic, muscarinic M_1 and M_2 , dopamine D_1 and D_2 , and GABA $_A$ and GABA $_B$ receptors. KAA-276 concentration-dependently antagonized histamine-induced contractions of guinea pig ileum and trachea, an effect which was irreversible. It also dose-dependently inhibited histamine-induced bronchoconstriction in guinea pigs following intraduodenal ($ED_{80} = 1.38$ and 1.9 mg/kg at 2 and 4 h, respectively), oral ($ED_{80} = 1.74$, 2.31 and 2.21 mg/kg at 4, 8 and 24 h, respectively) and inhalation administration ($ED_{80} = 0.03$ - 0.09% at 0.5-8 h), exhibiting a rapid onset and long duration of effect. Currently in development for the treatment of bronchial asthma administered by the aerosol route.

SOURCE – Kissei.

REFERENCES

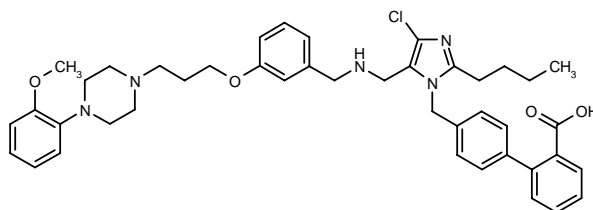
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2. Kobayashi, T. et al. Pharmacological characterization of a novel long-acting histamine H_1 receptor antagonist, KAA-276. Biol Pharm Bull 1998, 21(4): 350.
3. Kobayashi, T. et al. Disposition of 3H-KAA-276 after intratracheal administration to male rats. Xenobiotic Metab Dispos 1998, 13(1): 21.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

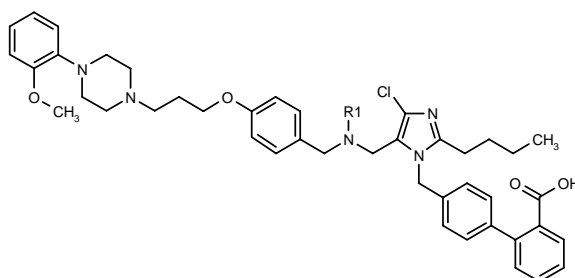
258422

4'-[2-Butyl-4-chloro-5-[3-[3-[4-(2-methoxy-phenyl)piperazin-1-yl]propoxy]benzylaminomethyl]-imidazol-1-ylmethyl]biphenyl-2-carboxylic acid



C43-H50-Cl-N5-O4; Mol wt: 736.35

ACTION – Antihypertensive agent with dual angiotensin II- and α_1 -adrenoceptor-antagonist activity, as demonstrated in functional assays by inhibition of angiotensin II- and phenylephrine-induced contractions of isolated rabbit aorta ($pA_2 = 8.1$ and 6.9 , respectively). Antihypertensive activity was shown *in vivo* in spontaneously hypertensive rats by a decrease in blood pressure of 42 mmHg when administered intragastrically at a dose of 30 mg. Other compounds from this series of imidazole derivatives include the following:



Compound	R1	Formula
263011	Me	C ₄₄ H ₅₂ ClN ₅ O ₄
263012	COBu	C ₄₈ H ₅₈ ClN ₅ O ₅

SOURCE – Kyorin.

REFERENCES

1. Kimura, T. et al. (Kyorin Pharm. Co., Ltd.) Novel imidazole derivs. having O-methoxyphenyl-piperazinylalkoxyaryl, and preparation method thereof. JP 97291078.

7. *TBC-1269 enters phase II for treatment and prevention of asthma.* Prous Science Daily Essentials October 24, 1997.

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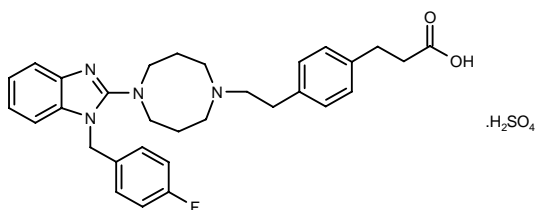
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*Identified compound **247672** Drug Data Rep 1997, 19(5): 414.

KAA-276

263124

3-[4-[2-[5-[1-(4-Fluorobenzyl)benzimidazol-2-yl]perhydro-1,5-diazocin-1-yl]ethyl]phenyl]propanoic acid sulfate



C31-H35-F-N4-O2.H2-S-O4; Mol wt: 612.71

ACTION – Potent and selective, nonsedating histamine H_1 receptor antagonist ($IC_{50} = 0.66$ nM for displacement of [3H]-mepyramine binding in guinea pig cerebellar membranes) with no significant affinity ($IC_{50} > 10,000$ nM) for α_1 -, α_2 -, β_1 - and β_2 -adrenoceptors, 5-HT $_1$ and 5-HT $_2$, histamine H_2 , nicotinic, muscarinic M_1 and M_2 , dopamine D_1 and D_2 , and GABA $_A$ and GABA $_B$ receptors. KAA-276 concentration-dependently antagonized histamine-induced contractions of guinea pig ileum and trachea, an effect which was irreversible. It also dose-dependently inhibited histamine-induced bronchoconstriction in guinea pigs following intraduodenal ($ED_{80} = 1.38$ and 1.9 mg/kg at 2 and 4 h, respectively), oral ($ED_{80} = 1.74$, 2.31 and 2.21 mg/kg at 4, 8 and 24 h, respectively) and inhalation administration ($ED_{80} = 0.03$ - 0.09% at 0.5 - 8 h), exhibiting a rapid onset and long duration of effect. Currently in development for the treatment of bronchial asthma administered by the aerosol route.

SOURCE – Kissei.

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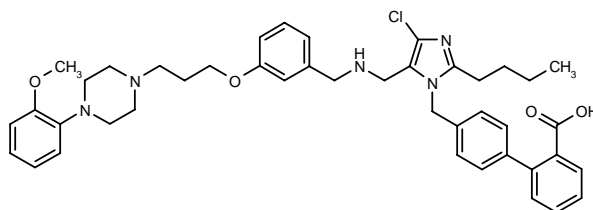
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3. Kobayashi, T. et al. Disposition of 3H-KAA-276 after intratracheal administration to male rats. Xenobiotic Metab Dispos 1998, 13(1): 21.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

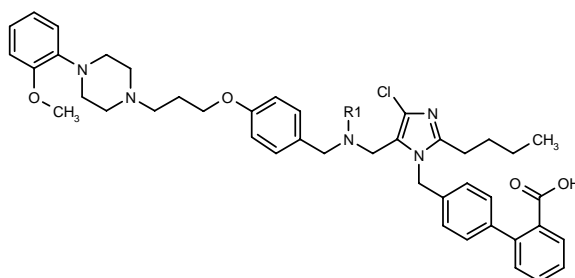
258422

4'-[2-Butyl-4-chloro-5-[3-[3-[4-(2-methoxy-phenyl)piperazin-1-yl]propoxy]benzylaminomethyl]-imidazol-1-ylmethyl]biphenyl-2-carboxylic acid



C43-H50-Cl-N5-O4; Mol wt: 736.35

ACTION – Antihypertensive agent with dual angiotensin II- and α_1 -adrenoceptor-antagonist activity, as demonstrated in functional assays by inhibition of angiotensin II- and phenylephrine-induced contractions of isolated rabbit aorta ($pA_2 = 8.1$ and 6.9 , respectively). Antihypertensive activity was shown *in vivo* in spontaneously hypertensive rats by a decrease in blood pressure of 42 mmHg when administered intragastrically at a dose of 30 mg. Other compounds from this series of imidazole derivatives include the following:



Compound	R1	Formula
263011	Me	C ₄₄ H ₅₂ ClN ₅ O ₄
263012	COBu	C ₄₈ H ₅₈ ClN ₅ O ₅

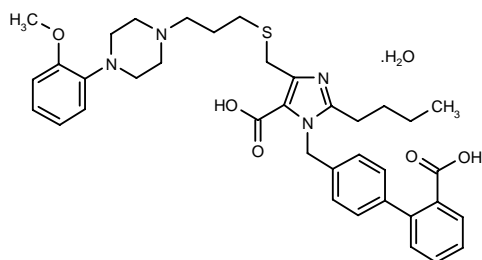
SOURCE – Kyorin.

REFERENCES

1. Kimura, T. et al. (Kyorin Pharm. Co., Ltd.) Novel imidazole derivs. having O-methoxyphenyl-piperazinylalkoxyaryl, and preparation method thereof. JP 97291078.

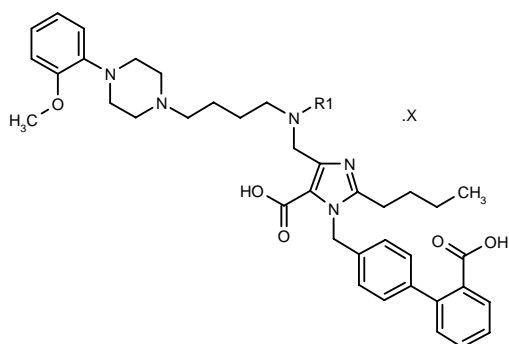
258423

2-Butyl-1-(2'-carboxybiphenyl-4-ylmethyl)-4-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propylsulfanylmethyl]-imidazole-5-carboxylic acid hydrate



C37-H44-N4-O5-S.H2O; Mol wt: 674.85

ACTION – Antihypertensive agent, an angiotensin II (All) receptor antagonist proven to potently and selectively inhibit All-induced rabbit thoracic aorta contractions ($pA_2 = 10.2$), while being much less potent when assessed for its α_1 -adrenoceptor-antagonist activity ($pA_2 = 6.1$ against phenylephrine-induced contractions). Compound produced a mean blood pressure reduction of 25 mmHg at a dose of 30 mg/kg p.o. in spontaneously hypertensive rats. Other representative compounds within this series of novel imidazole derivatives include the following:



Compound	R1	X	Formula
263144	Me		C ₃₉ H ₄₉ N ₅ O ₅
263145	H	H2O	C ₃₈ H ₄₇ N ₅ O ₅ ·H ₂ O

SOURCE – Kyorin.

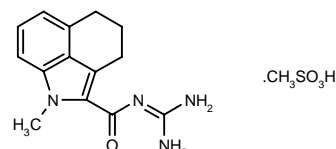
REFERENCES

1. Kimura, T. et al. (Kyorin Pharm. Co., Ltd.) *Novel imidazole derivs. having O-methoxyphenylpiperazidinyllalkyl on 4-position, and preparation method thereof.* JP 97291079.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

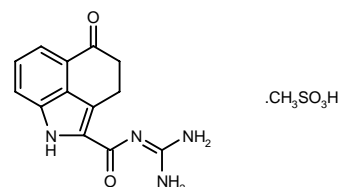
258421

N-(Diaminomethylene)-1-methyl-1,3,4,5-tetrahydrobenzo-[*cd*]indole-2-carboxamide methanesulfonate

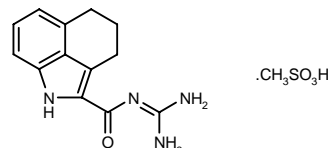


C14-H16-N4-O.C-H4-O3-S; Mol wt: 352.41

ACTION – Na⁺/H⁺ exchange inhibitor with an IC₅₀ value of 0.15 μM using isolated rat ventricular muscle cells. Other exemplified substituted guanidine derivatives include the following:



263146: C13-H12-N4-O2.C-H4-O3-S



263147: C13-H14-N4-O.C-H4-O3-S

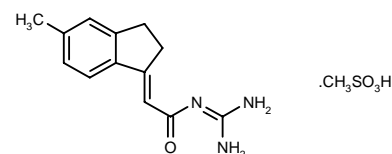
SOURCE – Sumitomo.

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1. Kitano, M. et al. (Sumitomo Pharm. Co., Ltd.) *Subst. guanidine derivs. and preparation method thereof.* EP 803501, JP 97291076.

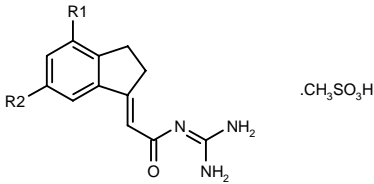
262077

N-[2-(5-Methylindan-1-ylidene)acetyl]guanidine methane-sulfonate



C13-H15-N3-O.C-H4-O3-S; Mol wt: 325.38

ACTION – Antiarrhythmic agent with cardioprotective activity, an inhibitor of Na⁺/H⁺ exchange, as demonstrated *in vitro* in rabbit erythrocytes. Potentially useful for the treatment or prevention of myocardial infarction, angina pectoris, cardiac arrhythmias and cardiac and cerebral ischemic disorders. Within this series of indanylidene-acetylguanidines, the following are also included:



Compound	R1	R2	Formula
263380	Me	H	C ₁₃ H ₁₅ N ₃ O·CH ₄ O ₃ S
263381	H	OMe	C ₁₃ H ₁₅ N ₃ O ₂ ·CH ₄ O ₃ S

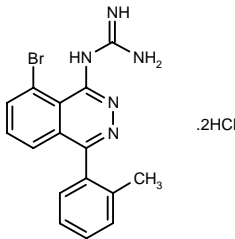
SOURCE – Hoechst Marion Roussel.

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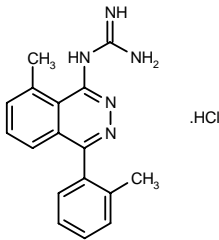
262092

N-[8-Bromo-4-(2-methylphenyl)phthalazin-1-yl]guanidine dihydrochloride



C16-H14-Br-N5.2HCl; Mol wt: 429.15

ACTION – Inhibitor of Na⁺/H⁺ exchange, as demonstrated in an *in vitro* test using rat platelet-rich plasma samples (78 and 62% inhibition, respectively, at 3 and 1 μM). Potentially useful for the treatment or prevention of myocardial ischemic disorders such as myocardial infarction or arrhythmia. Another specifically claimed condensed pyridazinyl guanidine is:



262846: C17-H17-N5.HCl

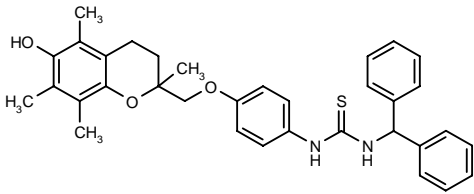
SOURCE – Takeda.

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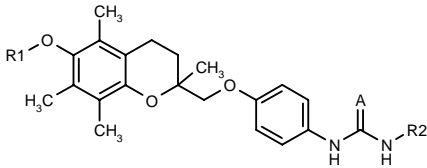
263163

N-(Diphenylmethyl)-N'-[4-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-ylmethoxy)phenyl]-thiourea



C34-H36-N2-O3-S; Mol wt: 552.73

ACTION – Agent for the treatment of atherosclerosis, inflammation, restenosis and immune disorders such as arthritis and transplant rejection, an antioxidant that also inhibits the expression of adhesion molecules such as VCAM-1 (IC₅₀ = 23.1 μM against TNF-induced VCAM-1 expression in human aortic endothelial cells) and ICAM-1. Within this series of chroman derivatives, the following are also included:



Compound	R1	R2	A	Formula
263399	H	t-Bu	S	C ₂₅ H ₃₄ N ₂ O ₃ S
263400	H	CH(Ph) ₂	O	C ₃₄ H ₃₆ N ₂ O ₄
263401	CH ₂ Ph	CH(Ph) ₂	S	C ₄₁ H ₄₂ N ₂ O ₃ S
263402	H	3-MeO-Ph	S	C ₂₈ H ₃₂ N ₂ O ₄ S

SOURCE – Warner-Lambert.

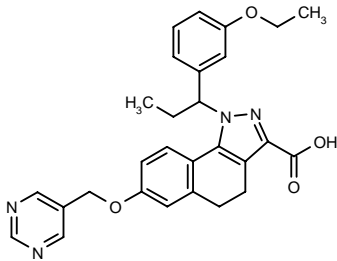
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ATZ-1993

261671

1-[1-(3-Ethoxyphenyl)propyl]-7-(pyrimidin-5-ylmethoxy)-4,5-dihydro-1H-naphtho[1,2-c]pyrazole-3-carboxylic acid



C28-H28-N4-O4; Mol wt: 484.55

ACTION – Potent, competitive and orally active endothelin, particularly ET_A receptor antagonist (IC₅₀ = 4.52 and 153.0 nM, respectively, against [¹²⁵I]-ET-1 binding at ET_A [porcine aorta] and ET_B [human placenta] receptors). Compound significantly inhibited intimal hyperplasia after endothelial denudation of the rabbit carotid artery at 30 mg/kg/day p.o. for 7 weeks, without affecting mean arterial blood pressure or heart rate; it also normalized impaired endothelium-dependent relaxation in hyperplastic aortic strips in this model. Its inhibitory effect on intimal hyperplasia appears to be mediated by both ET receptor antagonism and also through sustained activation of apoptosis resulting from selective inhibition of phosphodiesterase type III (PDE III; IC₅₀ = 75 nM using enzyme from guinea pig heart).

SOURCE – Teikoku Hormone.

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3. Yamashita, H. et al. *Search and study of novel non-peptide endothelin (ET) antagonists. Structure activity relationship of naphthopyrazole derivatives*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 01(XD)13-5.

EPLERENONE

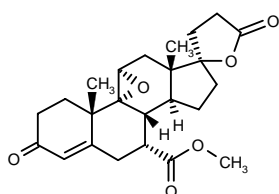
Prop INN; USAN

261466

9 α ,11 α -Epoxy-3,5'-dioxospiro[androst-4-ene-17,2'(*R*)-tetrahydrofuran]-7 α -carboxylic acid methyl ester

9 α ,11 α -Epoxy-17 β -hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone 7-methyl ester

SC-66110



C24-H30-O6; Mol wt: 414.50

ACTION – Highly selective aldosterone antagonist with a specificity profile superior to that of spironolactone, potentially useful for the treatment of hypertension and cardiac fibrosis, as well as heart failure. In a model of aldosterone-induced hypertension and cardiac fibrosis in uninephrectomized rats, administration of eplerenone provided modest protection against hypertension but was highly effective in preventing the development of cardiac fibrosis. The compound has also undergone clinical evaluation for the treatment of chronic liver disease and cirrhosis.

SOURCE – Searle.

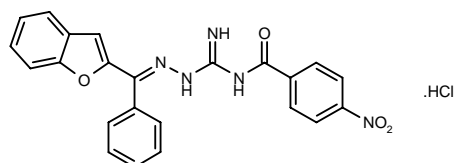
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2. Egan, J.J. et al. (G.D. Searle & Co.) *Method to treat cardiofibrosis with a combination therapy of an angiotensin II antagonist and an epoxy-steroidal aldosterone antagonist*. WO 9640255.
3. Ng, J.S. et al. (G.D. Searle & Co.) *Process for preparation of 7 α -carboxyl 9,11-epoxy steroids and intermediates useful therein and a general process for the epoxidation of olfinic double bonds*. WO 9721720.
4. Delyani, J. et al. *Eplerenone (SC 66110), a highly selective aldosterone antagonist*. Amer J Hypertension 1998, 11(4, Part 2): 94A.
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6. *Proposed international nonproprietary names: List No. 77*. WHO Drug Inform 1997, 11(2): 90.

ANTIARRHYTHMIC DRUGS

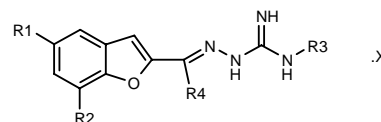
263160

1-[1-(Benzofuran-2-yl)-1-phenylmethyleamino]-3-(4-nitrobenzoyl)guanidine hydrochloride



C23-H17-N5-O4.HCl; Mol wt: 463.88

ACTION – Class III antiarrhythmic agent that causes a prolongation of the action potential duration and thereby increases the effective refractory period, without influencing other parameters of the action potential, i.e., maximum diastolic potential, maximum spread rate and action potential amplitude. Like amiodarone, test compound does not show reverse use-dependence. Other representative compounds within this series of amidinohydrazones include the following:



Compound	R1	R2	R3	R4	X	Formula
263395	H	H	Ph	4-(MeSO2NH)-Ph	HNO3	C ₂₃ H ₂₁ N ₅ O ₃ S .HNO ₃
263396	Br	H	H	2-benzofuryl	HCl	C ₁₈ H ₁₃ BrN ₄ O ₂ .HCl
263397	Br	H	COPh	Ph		C ₂₃ H ₁₇ BrN ₄ O ₂
263398	Br	Br	COPh	Ph		C ₂₃ H ₁₆ Br ₂ N ₄ O ₂

SOURCE – Helopharm.

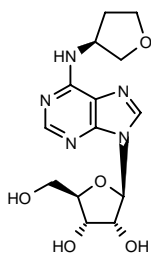
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CVT-510

252682

*N*⁶-[3(*S*)-Tetrahydrofuranyl]adenosine



C14-H19-N5-O5; Mol wt: 337.33

ACTION – Adenosine receptor agonist with selectivity for A₁ (K_i = 6.5 ± 1.4 nM in pig forebrain membranes) versus A_{2A} receptors (K_i = 2315 ± 650 nM in pig striatum membranes); in functional studies in guinea pig isolated perfused hearts, compound prolonged the S-H interval (A₁ response; EC₅₀ = 41.3 ± 2.0 nM) and increased coronary conductance (A_{2A} response; EC₅₀ = 200.5 ± 14.9 nM). In anesthetized closed-chest guinea pigs, a dose of 5.3 µg/kg/min caused second-degree AV block and a reduction in the mean arterial blood pressure of 50%. It is suggested that its negative dromotropic effect and A₁ selectivity will confer antiarrhythmic activity without hypotension.

SOURCE – CV Therapeutics.

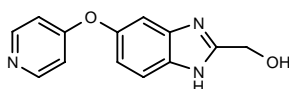
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MISCELLANEOUS CARDIOVASCULAR DRUGS

260881

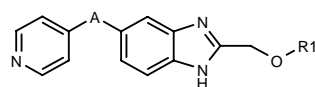
[5-(4-Pyridyloxy)-1*H*-benzimidazol-2-yl]methanol



C13-H11-N3-O2; Mol wt: 241.25

ACTION – Inhibitor of IL-1β production reported to be active in reducing tumor necrosis factor-α (TNF-α) levels in a mouse model of endotoxic shock induced by lipopolysaccharide (LPS). A representative compound from a series of benzimidazole, benzoxazole and

benzothiazole derivatives, wherein the following are also specifically claimed:



Compound	R1	A	Formula
263376	Ph	-S-	C ₁₉ H ₁₅ N ₃ OS
263377	Ph	-N(Me)-	C ₂₀ H ₁₈ N ₄ O
263378	H	-CH2O-	C ₁₄ H ₁₃ N ₃ O ₂

SOURCE – ADIR.

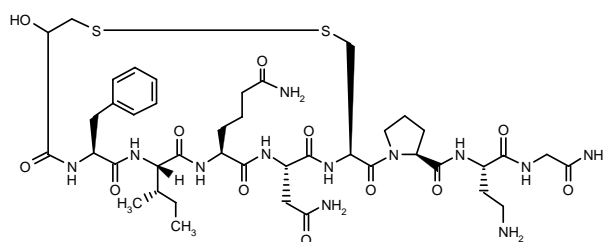
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F-180*

183294

2-Hydroxy-3-mercaptopropionyl-phenylalanyl-isoleucyl-homoglutaminy-asparginyl-cysteinyl-prolyl-L-(2,4-diaminobutryl)-glycinamide cyclic disulfide



C42-H64-N12-O12-S2; Mol wt: 993.16

ACTION – A long-acting vasopressin analog with selective agonist effects on vascular V_{1A} receptors and negligible effects on V₂ receptors. Compound displayed a vasopressor effect in portal hypertensive rats with partial portal vein ligation (PPVL; ED₅₀ = 0.54 nmol/kg i.v.) and in normal rats (ED₅₀ = 0.27 nmol/kg i.v.). A bolus injection of 0.405 nmol/kg significantly reduced portal pressure (13.8%) and superior mesenteric artery blood flow (25.6%) in PPVL; these effects were similar to those after i.v. infusion of vasopressin at 10 mU/kg, but the latter caused a significantly greater elevation in systemic vascular resistance and mean arterial pressure, and a more pronounced reduction in cardiac index. Potentially useful of the treatment for bleeding esophageal varices and other conditions requiring selective splanchnic vasoconstriction.

SOURCE – Ferring.

REFERENCES

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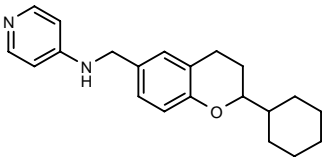
*Identified compound **183294** (see **176396**) Drug Data Rep 1992, 14(5): 418.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

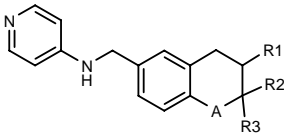
263238

N-(2-Cyclohexyl-3,4-dihydro-2*H*-1-benzopyran-6-yl-methyl)-*N*-(4-pyridyl)amine

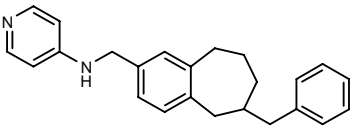


C21-H26-N2-O; Mol wt: 322.45

ACTION – Anticoagulant and antithrombotic agent with thrombin-inhibitory activity. A representative compound from a series of 4-pyridylamino derivatives, wherein the following are also included:



Compound	R1	R2	R3	A	Formula
263607	H	Ph	H	O	C ₂₁ H ₂₀ N ₂ O
263608	H	CH2Ph	H	O	C ₂₂ H ₂₂ N ₂ O
263609	H	cyclohexyl-CH2	H	O	C ₂₂ H ₂₈ N ₂ O
263610	H	cyclohexyl-CH2	Me	O	C ₂₃ H ₃₀ N ₂ O
263611	Me	cyclohexyl-CH2	H	O	C ₂₃ H ₃₀ N ₂ O
263612	H	CH2Ph	H	CH2	C ₂₃ H ₂₄ N ₂



263613: C24-H26-N2

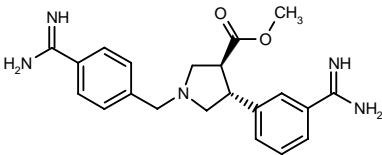
SOURCE – Merck & Co.

REFERENCES

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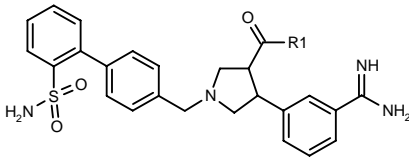
263248

trans-1-(4-Amidinobenzyl)-4-(3-amidinophenyl)-pyrrolidine-3-carboxylic acid methyl ester

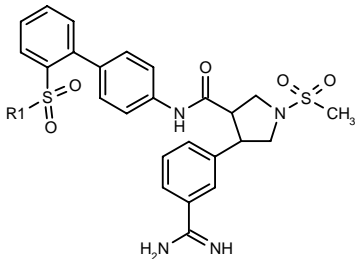


C21-H25-N5-O2; Mol wt: 379.46

ACTION – Anticoagulant, an inhibitor of trypsin-like serine protease enzymes, especially factor Xa. Within this series of specifically claimed amidinophenyl-pyrrolidines, -pyrrolines and -isoxazolidines, the following are also included:



Compound	R1	Isomer	Formula
264521	OMe	trans	C ₂₆ H ₂₈ N ₄ O ₄ S
264522	OMe	3 <i>S</i> ,4 <i>R</i>	C ₂₆ H ₂₈ N ₄ O ₄ S
264523	OMe	3 <i>R</i> ,4 <i>S</i>	C ₂₆ H ₂₈ N ₄ O ₄ S
264524	OH	trans	C ₂₅ H ₂₆ N ₄ O ₄ S
264525	NH2	trans	C ₂₅ H ₂₇ N ₅ O ₃ S



Compound	R1	Isomer	Formula
264526	NH2	trans	C ₂₈ H ₂₇ N ₅ O ₅ S ₂
264527	t-BuNH	trans	C ₂₉ H ₃₅ N ₅ O ₅ S ₂
264528	NH2	cis	C ₂₅ H ₂₇ N ₅ O ₅ S ₂

SOURCE – DuPont Merck.

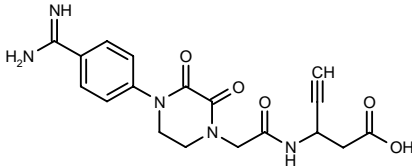
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ANTIPLATELET THERAPY

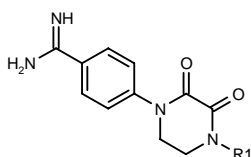
258424

3-[2-[4-(4-Amidinophenyl)-2,3-dioxopiperazin-1-yl]-acetamido]-4-pentynoic acid



C18-H19-N5-O5; Mol wt: 385.38

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist proven to inhibit ADP-induced aggregation of human platelet-rich plasma (PRP; IC₅₀ = 0.14 μM). A representative compound from a series of 2,3-diketopiperazine derivatives, wherein the following are also included:



Compound	R1	Formula
263219	CH ₂ CONHCH(Ph)CH ₂ CO ₂ H	C ₂₂ H ₂₃ N ₅ O ₅
263220	CH ₂ CONHCH(Me)CH ₂ CO ₂ H	C ₁₇ H ₂₁ N ₅ O ₅
263221	CH ₂ CONHCH(3-Pyr)CH ₂ CO ₂ H	C ₂₁ H ₂₂ N ₆ O ₅
263222	CH ₂ CH ₂ CONHCH(3-Pyr)CH ₂ CO ₂ H	C ₂₂ H ₂₄ N ₆ O ₅
263223	4-(CH ₂ CO ₂ H)-1-Pip-COCH ₂	C ₂₀ H ₂₅ N ₅ O ₅
264273	4-(CH ₂ CO ₂ H)-1-Piz-COCH ₂	C ₁₉ H ₂₄ N ₆ O ₅

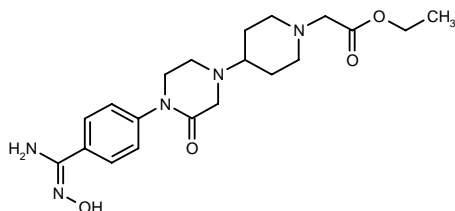
SOURCE – Toyama.

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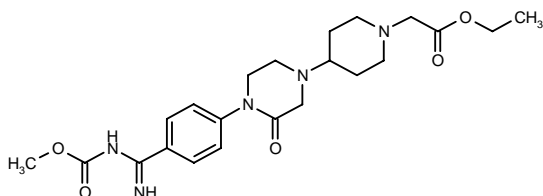
259900

2-[4-[4-[4-(*N*-Hydroxyamidino)phenyl]-3-oxopiperazin-1-yl]piperidin-1-yl]acetic acid ethyl ester



C20-H29-N5-O4; Mol wt: 403.48

ACTION – Platelet aggregation inhibitor, a gpIIb/IIIa (fibrinogen) receptor antagonist, an orally active prodrug of a known compound (241633*). Another representative compound within this series of substituted amidino-benzene derivatives is:



262716: C22-H31-N5-O5

SOURCES – Merck KGaA; Yamanouchi.

REFERENCES

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*See **240957** Drug Data Rep 1997, 19(1): 47.

EPTIFIBATIDE

Prop INN

190747

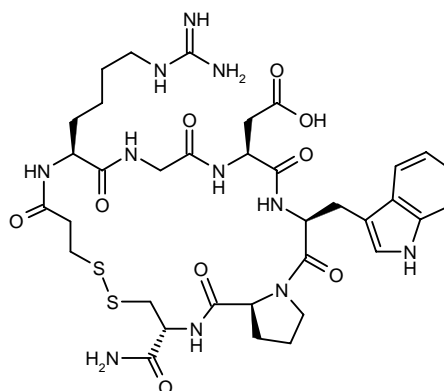
*N*⁶-(Aminoiminomethyl)-*N*²-(3-sulfanyl-1-oxopropyl)-L-lysyl-glycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide cyclic(1→6)-disulfide

C68-22

Intrifiban (former name)

SB-1

Sch-60936



C35-H49-N11-O9-S2; Mol wt: 831.96

ACTION – Platelet aggregation inhibitor, a heptapeptide platelet fibrinogen (gpIIb/IIIa) receptor antagonist.

INDICATION – Treatment of acute coronary syndrome (unstable angina and non-Q wave myocardial infarction) including patients who are to be managed medically and those undergoing percutaneous coronary intervention.

PRESENTATION – Solution for injection, 10 ml containing 20 mg eptifibatide (2 mg/ml) and 100 ml containing 75 mg eptifibatide (0.75 mg/ml).

PROPRIETARY NAME – *Integrilin*⁺ (US).

SOURCES – Cor Therapeutics; comarketed by Schering-Plough.

RECENT REFERENCES

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10. Lincoff, A.M. et al. *Clinical efficacy of Integrilin in unstable angina is accompanied by a modest increase in hemorrhagic risk: The PURSUIT trial.* J Amer Coll Cardiol 1998, 31(2, Suppl. A): Abst 837-4.

11. McClure, M. et al. *Thrombocytopenia in a large, international trial of the GP IIb/IIIa inhibitor eptifibatide in patients with acute coronary syndromes.* J Amer Coll Cardiol 1998, 31(2, Suppl. A): Abst 1028-107.

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29. *Cor Therapeutics submits NDA amendment for Integrilin for FDA.* Prous Science Daily Essentials October 2, 1997.

30. *Eptifibatide launch.* Cor Therapeutics, Inc. Company Communication 1998, May 19.

31. *FDA advisory committee recommends Integrilin approval.* Prous Science Daily Essentials January 29, 1998.

32. *FDA says Integrilin is approvable.* Prous Science Daily Essentials April 3, 1998.

33. *Integrilin™ available week of June 1st.* Cor Therapeutics, Inc. Company Communication 1998, May 27.

34. *Integrilin - First heart drug in its class approved for both acute coronary syndrome and angioplasty.* Cor Therapeutics, Inc. Company Communication 1998, May 18.

35. *Integrilin launched in first market today.* Prous Science Daily Essentials June 1, 1998.

36. *Integrilin to be reviewed by FDA advisory panel.* Prous Science Daily Essentials December 11, 1997.

37. *Two NDAs up for review this week by Cardiovascular and Renal Drugs Advisory Committee.* Prous Science Daily Essentials January 26, 1998.

MONOGRAPH – Scarborough, R.M. *Eptifibatide.* Drugs Fut 1998, 23(6): 585.

*Drug Data Rep 1993, 15(2): 166.

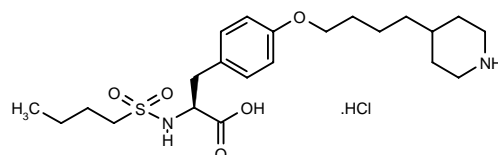
TIROFIBAN HYDROCHLORIDE

Prop INNM; USAN

183737

N-(Butylsulfonyl)-4-O-[4-(4-piperidyl)butyl]-L-tyrosine monohydrochloride

L-700462⁺
MK-383



C22-H36-N2-O5-S.HCl; Mol wt: 477.06

ACTION – Platelet aggregation inhibitor, a nonpeptide fibrinogen (gpIIb/IIIa) receptor antagonist.

INDICATION – Treatment of acute coronary syndrome including patients who are to be managed medically and those undergoing PTCA or atherectomy, in combination with heparin.

PRESENTATION – Premixed solution for injection, 500 ml containing 28.09 mg tirofiban hydrochloride monohydrate equiv. to 25 mg tirofiban (50 µg/ml); concentrated solution for i.v. infusion after dilution (50 ml), each ml containing 0.281 mg tirofiban hydrochloride monohydrate equiv. to 0.25 mg tirofiban (250 µg/ml).

PROPRIETARY NAME – Aggrastat (US).

SOURCE – Merck & Co.

RECENT REFERENCES

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13. RESTORE Economic Study Group. *Analysis of hospital costs and outcomes in RESTORE.* J Amer Coll Cardiol 1997, 29(2, Suppl. A): Abst 801-3.

14. Sax, F.L. *Clinical trials with Aggrastat in unstable angina.* IBC 8th Annu Int Symp Adv Anticoagulant Antithrombotic Thrombolytic Drugs (Oct 20-22, Cambridge) 1997.

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18. White, H.D. et al. *The effect of tirofiban vs heparin in patients presenting with non-Q-wave myocardial infarction.* Circulation 1997, 96(8, Suppl.): Abst 2643.

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21. Aggrastat® is first “platelet blocker” drug approved for treatment of unstable angina, a condition that can lead to heart attack. Merck & Co., Inc. Press Release 1998, May 14.

22. *FDA advisory committee recommends approval of Aggrastat.* Prous Science Daily Essentials May 4, 1998.

23. *FDA advisory committee will discuss Aggrastat NDA later this week.* Prous Science Daily Essentials April 7, 1998.

24. *FDA approves Aggrastat, the first platelet blocker for unstable angina.* Prous Science Daily Essentials May 22, 1998.

25. *First launch for Aggrastat, a new antiplatelet agent for acute coronary syndrome.* Prous Science Daily Essentials May 26, 1998.

26. *Merck & Co. reports new product candidate and pipeline overview.* Prous Science Daily Essentials December 12, 1997.

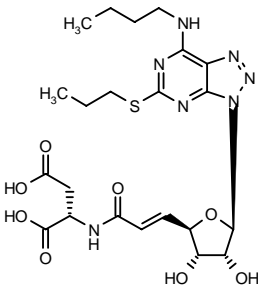
27. *Tirofiban HCl launch.* Merck & Co., Inc. Company Communication 1998, May 22.

MONOGRAPH – Hartman, G.D. *Tirofiban hydrochloride.* Drugs Fut 1995, 20(9): 897.

*Drug Data Rep 1992, 14(10): 891.

263158

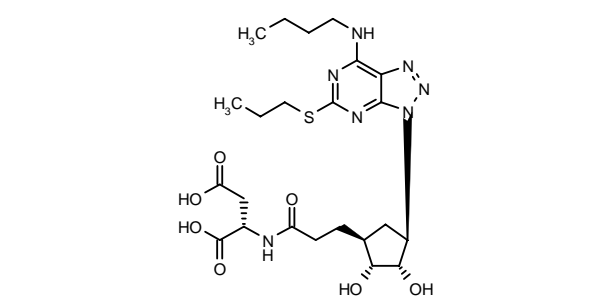
(E)-N-[1-[7-(Butylamino)-5-(propylsulfanyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-1,5,6-trideoxy-β-D-ribo-hept-5-enofuranuronoyl]-L-aspartic acid



C22-H31-N7-O8-S; Mol wt: 553.59

ACTION – Platelet aggregation inhibitor and anti-thrombotic agent that acts as an antagonist of the P2T purinoceptor and is expected to show improved efficacy compared to aspirin and reduced bleeding side effects compared to fibrinogen antagonists. Other specifically claimed compounds from this series of substituted triazolo[4,5-d]pyrimidines include the following:

Compound	R1	R2	R3	Formula
263393	Bu	Me	H	C ₂₅ H ₃₇ N ₇ O ₇ S
263394	SMe	CF3	NH4 ⁺	C ₂₂ H ₂₈ F ₃ N ₇ O ₇ S ₂ .NH ₃



263392: C23-H35-N7-O7-S

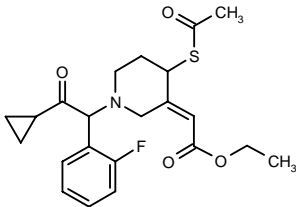
SOURCE – Astra.

REFERENCES

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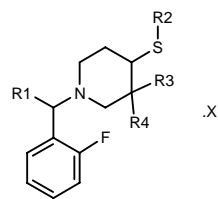
263337

2-[4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidin-3-ylidene]acetic acid ethyl ester



C22-H26-F-N-O4-S; Mol wt: 419.51

ACTION – Platelet aggregation inhibitor that shows strong *ex vivo* inhibitory effects (> 85-90%) in experiments in rats using ADP or collagen as the inducers of platelet aggregation. Activity was also demonstrated *in vivo* by the ability to prolong bleeding time in mice. Within this series of cyclic amine derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
264062	cyclopropyl-CO	H	H	H	HCl	C ₁₆ H ₂₀ FNOS .HCl
264063	Pr	H	-CH[CON(Me)2]-			C ₁₉ H ₂₇ FN ₂ OS
264064	cyclopropyl-CO	Ac	-CH[CON(Me)2]-			C ₂₂ H ₂₇ FN ₂ O ₃ S

SOURCES – Sankyo; Ube.

REFERENCES

1. Asai, F. et al. (Sankyo Co., Ltd.; Ube Ind., Ltd.) *Cyclic amine derivs.* JP 98120649, WO 9808811.

CLOPIDOGREL HYDROGENSULFATE

Rec INN; BANM

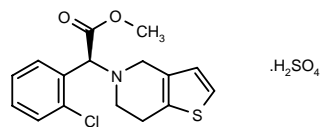
142672

(+)-(S)-2-(2-Chlorophenyl)-2-(4,5,6,7-tetrahydrothieno-[3,2-c]pyridin-5-yl)acetic acid methyl ester hydrogen-sulfate

Clopidogrel bisulfate (USAN)

DV-7314

SR-25990C⁺



C16-H16-Cl-N-O2-S.H2-S-O4; Mol wt: 419.89

ACTION – Inhibitor of ADP-induced platelet aggregation that acts by inhibiting the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the gpIIb/IIIa complex. It also inhibits platelet aggregation induced by other agonists.

INDICATION – Reduction of atherosclerotic events in patients with atherosclerosis documented by recent myocardial infarction, recent stroke or established peripheral arterial disease.

PRESENTATION – Tablets, 97.875 mg clopidogrel bisulfate equiv. to 75 mg base.

PROPRIETARY NAME – *Plavix* (US).

SOURCES – Bristol-Myers Squibb; Sanofi.

RECENT REFERENCES

1. Anderson, H.V. et al. *Platelet inhibition with oral antagonists to thromboxane, serotonin, and ADP reduces neointimal proliferation in a hypercholesterolemic canine coronary angioplasty model.* J Amer Coll Cardiol 1997, 29(2, Suppl. A): Abst 701-3.

2. Biller, J. et al. *Number of major vascular events prevented by clopidogrel vs. other cardiovascular therapies.* 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst P03.085.

3. Bousser, M.G. et al. *Ticlopidine and clopidogrel in secondary stroke prevention.* Cerebrovasc Dis 1997, 7(Suppl. 6): 17.

4. Ferguson, J.J. et al. *Roundtable discussion: Clinical safety and efficacy of clopidogrel - Implications of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study for future management of atherosclerotic disease.* Clin Ther 1998, 20(Suppl. B): B42.

5. Fisher, L.D. *Active control trials: What about a placebo? A method illustrated with clopidogrel, aspirin and placebo.* J Amer Coll Cardiol 1998, 31(2, Suppl. A): Abst 1026-68.

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7. Hampton, J.R. *Effect of clopidogrel on patients with a previous myocardial infarction: The CAPRIE study.* J Amer Coll Cardiol 1998, 31(5, Suppl. C): Abst 1910.

8. Harker, L.A. et al. *Antithrombotic effects of aspirin and clopidogrel for stent, graft and vascular thrombosis in baboons.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 1884.

9. Hoek, J. *Clopidogrel: An advance in antithrombotic therapy.* IBC 8th Annu Int Symp Adv Anticoagulant Antithrombotic Thrombolytic Drugs (Oct 20-22, Cambridge) 1997.

10. Leray, C. et al. *Effects of clopidogrel and its inactive form, SR 25989, on plasma, liver and platelet lipids in the rat.* Platelets 1998, 9(1): 49.

11. Makkar, R. et al. *Clopidogrel, a novel platelet ADP-receptor antagonist inhibits aspirin and ticlopidine-resistant stent thrombosis.* J Amer Coll Cardiol 1997, 29(2, Suppl. A): Abst 771-3.

12. Mills, D.C.B. and Agelan, A. *The effect of the anti thrombotic agent, clopidogrel on ADP receptors on rat platelets revealed by photoaffinity labelling with AzPET-ADP.* Thromb Haemost 1997, Suppl.: Abst PS-1899.

13. Weber, A.A. and Schror, K. *Pharmacology of ticlopidine and clopidogrel in comparison with acetylsalicylic acid.* Internist 1997, 38(11): 1115.

14. *Advisory committee recommends approval for Plavix.* Prous Science Daily Essentials October 29, 1997.

15. *Bristol-Myers and Sanofi file in the U.S. and Europe for approval of new antithrombotic drug.* Bristol-Myers Squibb Press Release 1997, May 5.

16. *Bristol-Myers Squibb: Q3 1997 highlights.* Prous Science Daily Essentials November 18, 1997.

17. *FDA clears Plavix.* Prous Science Daily Essentials November 19, 1997.

18. *Plavix® (clopidogrel bisulfate), a new antiplatelet agent from Sanofi research, is cleared for marketing in the US.* Sanofi Pharmaceuticals, Inc. Press Release 1997, November 18.

19. *Plavix launch.* Sanofi Pharmaceuticals, Inc. Company Communication 1998, May 21.

20. *Sanofi and Bristol-Myers Squibb receive clearance to market Plavix®.* Sanofi Pharmaceuticals, Inc. Bristol-Myers Squibb Co. 1997, November 18.

21. *U.S. market introduction announced for Plavix.* Prous Science Daily Essentials May 22, 1998.

MONOGRAPH – Herbert, J.M. et al. *Clopidogrel hydrogensulfate.* Drugs Fut 1993, 18(2): 107.

*Drug Data Rep 1988, 10(8): 649.

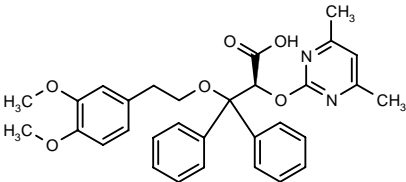
RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

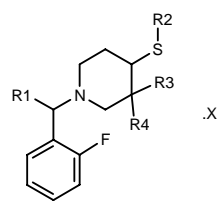
LU-302872

264159

(S)-3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-(4,6-dimethyl-pyrimidin-2-yl)-3,3-diphenylpropionic acid



C31-H32-N2-O6; Mol wt: 528.60



Compound	R1	R2	R3	R4	X	Formula
264062	cyclopropyl-CO	H	H	H	HCl	C ₁₆ H ₂₀ FNOS .HCl
264063	Pr	H	-CH[CON(Me)2]-			C ₁₉ H ₂₇ FN ₂ OS
264064	cyclopropyl-CO	Ac	-CH[CON(Me)2]-			C ₂₂ H ₂₇ FN ₂ O ₃ S

SOURCES – Sankyo; Ube.

REFERENCES

1. Asai, F. et al. (Sankyo Co., Ltd.; Ube Ind., Ltd.) *Cyclic amine derivs.* JP 98120649, WO 9808811.

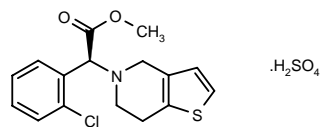
CLOPIDOGREL HYDROGENSULFATE

Rec INN; BANM

142672

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Clopidogrel bisulfate (USAN)
DV-7314
SR-25990C⁺



C16-H16-Cl-N-O2-S.H2-S-O4; Mol wt: 419.89

ACTION – Inhibitor of ADP-induced platelet aggregation that acts by inhibiting the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the gpIIb/IIIa complex. It also inhibits platelet aggregation induced by other agonists.

INDICATION – Reduction of atherosclerotic events in patients with atherosclerosis documented by recent myocardial infarction, recent stroke or established peripheral arterial disease.

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8. Harker, L.A. et al. *Antithrombotic effects of aspirin and clopidogrel for stent, graft and vascular thrombosis in baboons.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 1884.

9. Hoek, J. *Clopidogrel: An advance in antithrombotic therapy.* IBC 8th Annu Int Symp Adv Anticoagulant Antithrombotic Thrombolytic Drugs (Oct 20-22, Cambridge) 1997.

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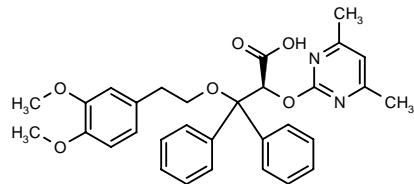
RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

LU-302872

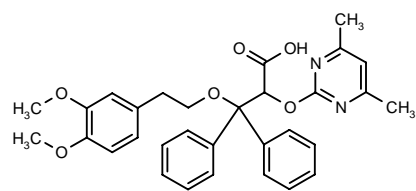
264159

(S)-3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-(4,6-dimethyl-pyrimidin-2-yl)-3,3-diphenylpropionic acid



C31-H32-N2-O6; Mol wt: 528.60

ACTION – Potent, orally active dual endothelin ET_A and ET_B receptor antagonist ($K_i = 2.2$ and 5.8 nmol/l, respectively, for human ET_A and ET_B receptors expressed in CHO cells), the active enantiomer of the racemate **LU-224332**. Title compound (10 mg/kg p.o.) inhibited the pressor response to ET-1 ($59 \pm 8\%$) in rats and bronchospasm in guinea pigs induced by ET-1 ($78 \pm 7\%$). The compound ($1 \mu\text{M}$) also inhibited ET-1-induced contractions in human prostate tissue. LU-302872 has been proposed as a suitable candidate for clinical testing in benign prostatic hyperplasia.



LU-224332 [264160]: C31-H32-N2-O6

SOURCE – Knoll.

REFERENCES

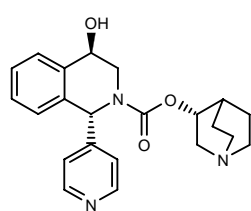
1. Raschack, M. et al. *The new ET_{A/B} receptor antagonist LU 302 872 shows high oral activity and inhibits human prostate contractions.* J Urol 1998, 159(5,Suppl.): Abst 1264.

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TREATMENT OF URINARY INCONTINENCE

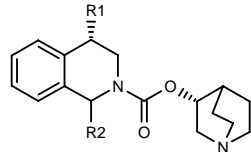
260523

4(*R*)-Hydroxy-1(*R*)-(4-pyridyl)-1,2,3,4-tetrahydro-isoquinoline-2-carboxylic acid quinuclidin-3(*R*)-yl ester



C22-H25-N3-O3; Mol wt: 379.46

ACTION – Agent for the treatment of disorders of the urinary, digestive and respiratory tract, a muscarinic M₃ receptor antagonist. Within this series of isoquinoline derivatives, the following are also included:



Compound	R1	R2	Isomer	Formula
263195	OH	3-thienyl	R	C ₂₁ H ₂₄ N ₂ O ₃ S
263196	OH	3-furyl	S	C ₂₁ H ₂₄ N ₂ O ₄
263197	OH	4-Me-Ph	R	C ₂₄ H ₂₈ N ₂ O ₃

Compound	R1	R2	Isomer	Formula
263198	OMe	Ph	S	C ₂₄ H ₂₈ N ₂ O ₃
263199	OMe	2-furyl	R	C ₂₂ H ₂₆ N ₂ O ₄
263200	OMe	4-Me-Ph	S	C ₂₅ H ₃₀ N ₂ O ₃
263201	Me	3-thienyl	R	C ₂₂ H ₂₆ N ₂ O ₂ S

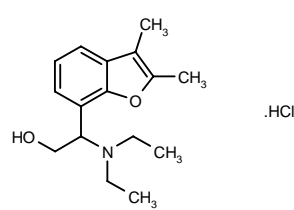
SOURCE – Yamanouchi.

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1. Naito, R. et al. (Yamanouchi Pharm. Co., Ltd.) *Novel isoquinoline derivs. or their salts.* JP 98007675.

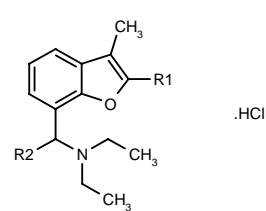
263354

2-(Diethylamino)-2-(2,3-dimethylbenzofuran-7-yl)ethanol hydrochloride



C16-H23-N-O2.HCl; Mol wt: 297.82

ACTION – Agent for the treatment of urinary incontinence with potent smooth muscle contractile activity, expected to be devoid of cardiovascular side effects by virtue of its selectivity for urethral over arterial smooth muscle, as demonstrated in *in vitro* and *in vivo* tests. Within this series of benzylamine derivatives, the following are also included:



Compound	R1	R2	Isomer	Formula
264313	Me	CH2N(Et)2		C ₂₀ H ₃₂ N ₂ O.HCl
264314	Me	CH2F		C ₁₆ H ₂₂ FNO.HCl
264315	Et	CH2OH		C ₁₇ H ₂₅ NO ₂ .HCl
264316	Me	Me		C ₁₆ H ₂₃ NO.HCl
264317	Et	CH2OH	(+)	C ₁₇ H ₂₅ NO ₂ .HCl

SOURCE – Synthélabo.

REFERENCES

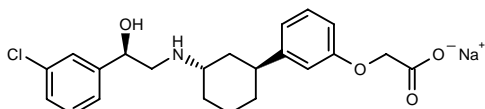
1. Philippo, C. et al. (Synthélabo) *Benzylamine derivs., their preparation and their application in therapeutics.* WO 9808834.

GS-332

251744

trans-2-[3-[3-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethyl-amino]cyclohexyl]phenoxy]acetic acid sodium salt

trans-2-[3'-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethylamino]-1',2',3',4',5',6'-hexahydrobiphenyl-3-yloxy]acetic acid sodium salt



C22-H25-Cl-N-Na-O4; Mol wt: 425.89

ACTION – Selective β_3 -adrenoceptor agonist with little β_1 - and β_2 -adrenoceptor activity. Compound exhibited potent relaxant effects on rat bladder, and may therefore be useful for the treatment of pollakiuria and urinary incontinence.

SOURCE – Tokyo Tanabe.

REFERENCES

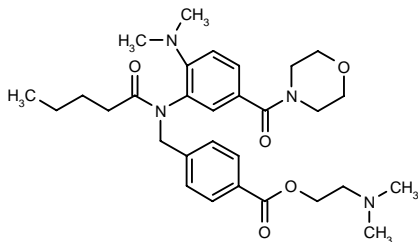
1. Tsuchiya, S. et al. (Tokyo Tanabe Co., Ltd.) *Phenylethanolamine cpds. useful as beta3 agonist, process for producing the same, and intermediates in the production of the same*. WO 9715549.

2. Matsumoto, H. et al. *Synthesis of GS-332, a selectively β_3 -adrenoceptor agonist, and pharmaceutical effect thereof*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XD)13-4.

TREATMENT OF RENAL DISEASES

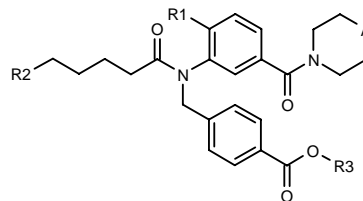
258440

4-[*N*-[2-(Dimethylamino)-5-(4-morpholinylcarbonyl)-phenyl]-*N*-pentanoylaminomethyl]benzoic acid 2-(dimethylamino)ethyl ester



C30-H42-N4-O5; Mol wt: 538.69

ACTION – Agent for the treatment of renal dysfunction with no significant angiotensin II receptor-antagonist activity and negligible antihypertensive activity in renal hypertensive rats at a dose of 20 mg/kg p.o. At this dose, compound improved kidney function in a renal disease model in rats, as demonstrated by a decrease in serum creatinine and urea nitrogen levels and an increase in creatinine clearance; compound was also shown to prolong survival time (7.5 weeks vs. 5.0 weeks in controls). No deaths were observed following a single dose of 500 mg/kg p.o. to mice. Within this series of benzene derivatives, the following are also included:



Compound	R1	R2	R3	A	Formula
263118	i-Pr	H	CH2CH2N(Me)2	O	C ₃₁ H ₄₃ N ₃ O ₅
263119	N(Me)2	H	H	N(Pr)	C ₂₉ H ₄₀ N ₄ O ₄
263120	N(Me)2	Et	H	N(Pr)	C ₃₁ H ₄₄ N ₄ O ₄
263121	i-Pr	Et	H	N(Me)	C ₃₀ H ₄₁ N ₃ O ₄
263122	i-Pr	H	H	N(Pr)	C ₃₀ H ₄₁ N ₃ O ₄
263123	i-Pr	Et	H	N(Pr)	C ₃₂ H ₄₅ N ₃ O ₄

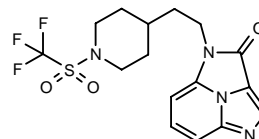
SOURCE – Kureha.

REFERENCES

1. Yanaka, M. et al. (Kureha Chem. Ind.) *Benzene derivs*. EP 807628, JP 97301944.

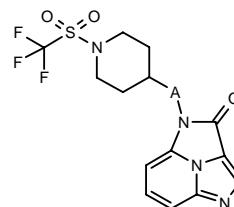
262104

1-[2-[1-(Trifluoromethylsulfonyl)piperidin-4-yl]ethyl]-1,4,7b-triazacyclopent[cd]inden-2(1*H*)-one

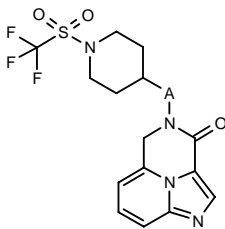


C16-H17-F3-N4-O3-S; Mol wt: 402.39

ACTION – Agent for the treatment or prevention of renal and cardiovascular disorders that displays marked platelet-derived growth factor (PDGF)-inhibitory activity, with 94.9% inhibition of PDGF-induced human skin fibroblast Hs62 cell proliferation at 0.3 μ M. At 1 mg/kg/day p.o. once daily for 6 weeks, compound markedly inhibited urinary protein excretion (total protein and albumin) in hypercholesterolemic rats, indicating potential in the treatment of chronic glomerulonephritis. Also claimed for use in the treatment or prevention of arteriosclerosis, restenosis following percutaneous transluminal coronary angioplasty (PTCA) and diabetic nephropathy, and for lowering lipid levels. Other specifically claimed tricyclic compounds include the following:



Compound	A	Formula
262877	-CH2-	C ₁₅ H ₁₅ F ₃ N ₄ O ₃ S
262878	-(CH2)3-	C ₁₇ H ₁₉ F ₃ N ₄ O ₃ S



Compound	A	Formula
262879	-CH2-	C ₁₆ H ₁₇ F ₃ N ₄ O ₃ S
262880	-(CH2)2-	C ₁₇ H ₁₉ F ₃ N ₄ O ₃ S

SOURCE – Takeda.

REFERENCES

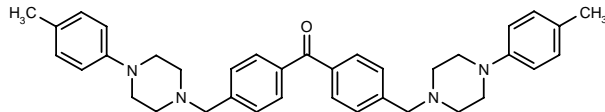
1. Kawamoto, T. et al. (Takeda Chem. Ind., Ltd.) *Tricyclic cpds., their production and use*. EP 826686, JP 98120568.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

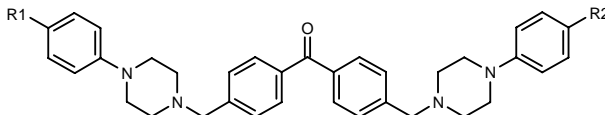
262804

4,4'-Bis[4-(4-methylphenyl)piperazin-1-ylmethyl]-benzophenone

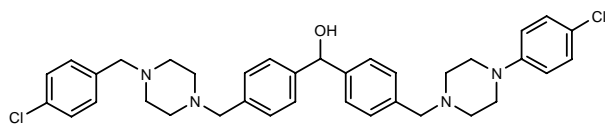


C37-H42-N4-O; Mol wt: 558.76

ACTION – Antiulcer agent with potent activity against *Helicobacter pylori*; compound exhibited MIC values of < 0.0008 µg/ml against *H. pylori* strains CPY 433 and TN 58 compared to MIC values of 6.25 and 3.13 µg/ml, respectively, for metronidazole. A representative compound from a series of cyclic amines, wherein the following are also included:



Compound	R1=R2	Formula
263108	F	C ₃₅ H ₃₆ F ₂ N ₄ O
263109	OMe	C ₃₇ H ₄₂ N ₄ O ₃
263110	Cl	C ₃₅ H ₃₆ Cl ₂ N ₄ O



263111: C36-H40-Cl2-N4-O

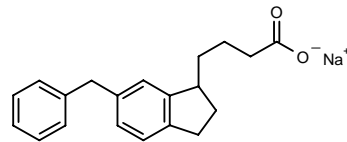
SOURCE – Takeda.

REFERENCES

1. Aono, T. et al. (Takeda Chem. Ind., Ltd.) *Cyclic amine derivs. and medicines containing the same*. JP 98059954.

262817

4-(6-Benzylindan-1-yl)butyric acid sodium salt



C20-H21-Na-O2; Mol wt: 316.37

ACTION – Antiulcer agent with selective antimicrobial activity against *Helicobacter pylori* (MIC = 32 µg/ml against *H. pylori* ATCC 43579) and little or no activity against other bacteria such as *Escherichia coli* ATCC 25922 (MIC > 2048 µg/ml) and *Staphylococcus aureus* ATCC 25923 (MIC = 128 µg/ml).

SOURCE – Sagami.

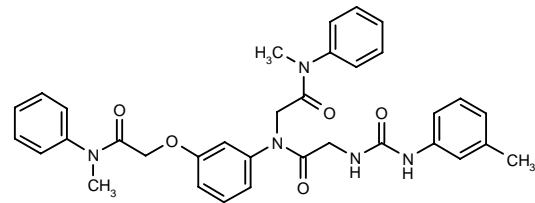
REFERENCES

1. Numao, N. et al. (Sagami Chem. Res. Center) *1,6-Disubst. indan derivs. and anti-Helicobacter pylori agents*. JP 98072390.

DZ-3514

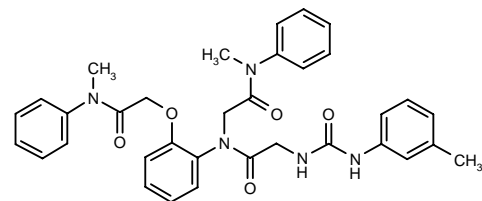
262025

N-Methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]-*N*-phenylacetamide

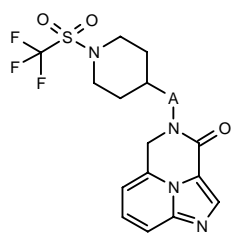


C34-H35-N5-O5; Mol wt: 593.68

ACTION – A potent gastrin/cholecystokinin CCK_B receptor antagonist (IC₅₀ = 0.8 nM against [¹²⁵I]-Tyr-gastrin binding to the human gastrin receptor expressed in CHO cells) with good selectivity over the CCK_A receptor (IC₅₀ = 178 nM against [¹²⁵I]-CCK-8 binding to the human receptor) and potential application in the treatment of digestive tract disorders such as peptic ulcer, or CNS disorders. Another compound from this series of phenoxyacetic acid derivatives is:



DA-3797 [263086]: C34-H35-N5-O5



Compound	A	Formula
262879	-CH2-	C ₁₆ H ₁₇ F ₃ N ₄ O ₃ S
262880	-(CH ₂) ₂ -	C ₁₇ H ₁₉ F ₃ N ₄ O ₃ S

SOURCE – Takeda.

REFERENCES

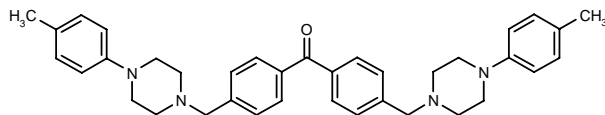
1. Kawamoto, T. et al. (Takeda Chem. Ind., Ltd.) *Tricyclic cpds., their production and use*. EP 826686, JP 98120568.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

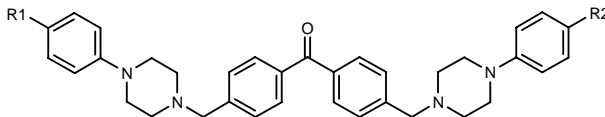
262804

4,4'-Bis[4-(4-methylphenyl)piperazin-1-ylmethyl]-benzophenone

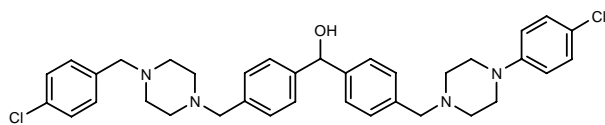


C37-H42-N4-O; Mol wt: 558.76

ACTION – Antiulcer agent with potent activity against *Helicobacter pylori*; compound exhibited MIC values of < 0.0008 µg/ml against *H. pylori* strains CPY 433 and TN 58 compared to MIC values of 6.25 and 3.13 µg/ml, respectively, for metronidazole. A representative compound from a series of cyclic amines, wherein the following are also included:



Compound	R1=R2	Formula
263108	F	C ₃₅ H ₃₆ F ₂ N ₄ O
263109	OMe	C ₃₇ H ₄₂ N ₄ O ₃
263110	Cl	C ₃₅ H ₃₆ Cl ₂ N ₄ O



263111: C36-H40-Cl2-N4-O

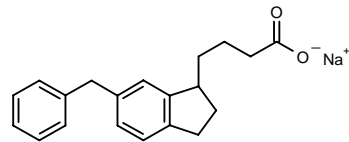
SOURCE – Takeda.

REFERENCES

1. Aono, T. et al. (Takeda Chem. Ind., Ltd.) *Cyclic amine derivs. and medicines containing the same*. JP 98059954.

262817

4-(6-Benzylindan-1-yl)butyric acid sodium salt



C20-H21-Na-O2; Mol wt: 316.37

ACTION – Antiulcer agent with selective antimicrobial activity against *Helicobacter pylori* (MIC = 32 µg/ml against *H. pylori* ATCC 43579) and little or no activity against other bacteria such as *Escherichia coli* ATCC 25922 (MIC > 2048 µg/ml) and *Staphylococcus aureus* ATCC 25923 (MIC = 128 µg/ml).

SOURCE – Sagami.

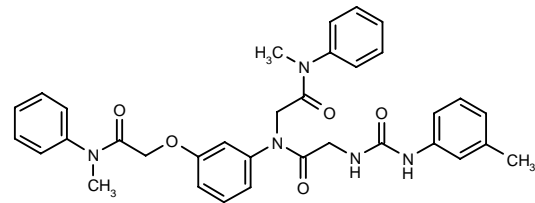
REFERENCES

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DZ-3514

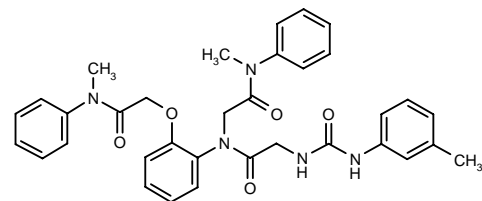
262025

N-Methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]-*N*-phenylacetamide



C34-H35-N5-O5; Mol wt: 593.68

ACTION – A potent gastrin/cholecystokinin CCK_B receptor antagonist (IC₅₀ = 0.8 nM against [¹²⁵I]-Tyr-gastrin binding to the human gastrin receptor expressed in CHO cells) with good selectivity over the CCK_A receptor (IC₅₀ = 178 nM against [¹²⁵I]-CCK-8 binding to the human receptor) and potential application in the treatment of digestive tract disorders such as peptic ulcer, or CNS disorders. Another compound from this series of phenoxyacetic acid derivatives is:



DA-3797 [263086]: C34-H35-N5-O5

SOURCE – Daiichi Pharm.

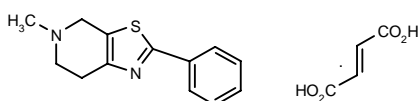
REFERENCES

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2. Takeda, Y. et al. *Synthesis of phenoxyacetic acid derivatives as highly potent antagonists of gastrin/cholecystokinin-B receptors.* Chem Pharm Bull 1998, 46(3): 434.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

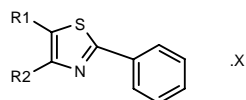
260541

5-Methyl-2-phenyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine fumarate



C13-H14-N2-S.C4-H4-O4; Mol wt: 346.40

ACTION – Gastric prokinetic agent that improves digestive tract motility via its antagonist effect at 5-HT₃ receptors. It was active at concentrations of < 300 µM in inhibiting 5-HT-induced guinea pig ileum contractions. Within this series of substituted thiazole derivatives, the following are also included:



Compound	R1	R2	X	Formula
263203	-CH2CH2N(Et)CH2-		oxalate	C ₁₄ H ₁₆ N ₂ S.C ₂ H ₂ O ₄
263204	-CH2CH2N(Me)CH2CH2-		fumarate	C ₁₄ H ₁₆ N ₂ S.C ₄ H ₄ O ₄
263205	-CH2CH2NHCH2CH2-		.2HCl.H2O	C ₁₃ H ₁₄ N ₂ S.2HCl.H ₂ O
263206	-CH2CH(NH2)CH2CH2-		fumarate	C ₁₃ H ₁₄ N ₂ S.C ₄ H ₄ O ₄
263207	-CH2CH[N(Me)2]CH2CH2-		fumarate	C ₁₅ H ₁₈ N ₂ S.C ₄ H ₄ O ₄
263208	H	CH2N(Me)2	fumarate	C ₁₂ H ₁₄ N ₂ S.C ₄ H ₄ O ₄

SOURCE – Yamanouchi.

REFERENCES

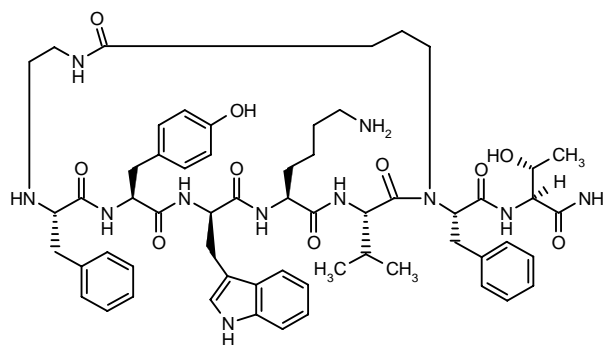
1. Iwaoka, K. et al. (Yamanouchi Pharm. Co., Ltd.) *Medicines containing substd. thiazole derivs. as effective ingredient and novel cpds.* JP 98017569.

TREATMENT OF PANCREATIC DISORDERS

PTR-3046

261761

[3S-(3α,6α,9β,12α,15α)]-2(S)-[6-(4-Aminobutyl)-15-benzyl-12-(4-hydroxybenzyl)-9-(1H-indol-3-ylmethyl)-3-isopropyl-2,5,8,11,14,20-hexaoxo-1,4,7,10,13,16,19-heptaazacyclotricosan-1-yl]-3-phenylpropionyl-L-threoninamide



C59-H77-N11-O10; Mol wt: 1100.32

ACTION – Somatostatin analog selective for sst5 receptors (IC₅₀ = 67 nM for displacement of [¹²⁵I]-Tyr¹¹-SRIF in human cloned receptors expressed in CHO cells; IC₅₀ > 1000 nM for cloned human sst1 and sst4 and mouse sst2 and sst3 receptors). Title compound (100 mg/kg s.c.), similar to octreotide, inhibited bombesin-induced pancreatic exocrine secretion in rats, and it also inhibited caerulein-induced pancreatic exocrine secretion (100 mg/kg by 2-h i.v. infusion), as well as pancreatic exocrine secretion in a duodenal perfusion model. However, in contrast to octreotide, it did not inhibit growth hormone or glucagon release induced by L-arginine. The compound was highly stable *in vitro* to enzymatic degradation when incubated with both rat renal homogenates and human serum. Potentially useful for the treatment of pancreatic disorders and other gastrointestinal disorders.

SOURCES – Peptor; Yissum.

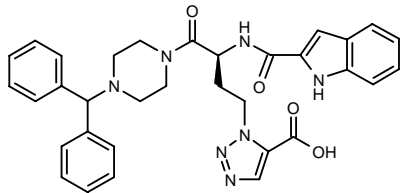
REFERENCES

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2. Gilon, C. et al. *A backbone-cyclic, receptor 5-selective somatostatin analogue: Synthesis, bioactivity, and nuclear magnetic resonance conformational analysis.* J Med Chem 1998, 41(6): 919.

TP-1202

262474

1-[4-[4-(Diphenylmethyl)piperazin-1-yl]-3(*S*)-(1*H*-indol-2-ylcarboxamido)-4-oxobutyl]-1,2,3-triazole-5-carboxylic acid



C33-H33-N7-O4; Mol wt: 591.67

ACTION – Agent for the treatment of pancreatitis, a selective CCK_A receptor antagonist (IC₅₀ = 0.037 μM) with reduced affinity for CCK_B receptors (IC₅₀ = 69 μM); the compound had an IC₅₀ value of 0.12 μM for inhibition of CCK-8-induced contractions in isolated guinea pig ileum.

SOURCE – Tobishi.

REFERENCES

1. Ogawa, M. et al. (Tobishi Pharm. Co., Ltd.) *Amino acid deriv. having anti-CKK activity*. EP 710661, JP 96119940, JP 96176144, US 5716958.

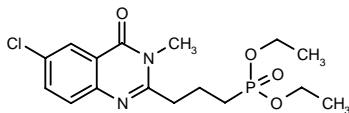
2. Matsuda, H. et al. *Synthesis and structure activity relationship of amino acid derivatives having CCK receptor antagonism (II)*. 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(XP)9-19.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

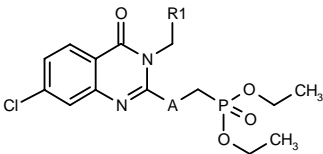
258415

3-(6-Chloro-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-propylphosphonic acid diethyl ester



C16-H22-Cl-N2-O4-P; Mol wt: 372.79

ACTION – Antidiabetic agent with potent blood glucose-lowering activity in rats (–83% at 100 mg/kg p.o. once daily for 4 consecutive days). Within this series of phosphonic acid diester derivatives, the following are also included:



Compound	R1	A	Formula
262900	H	-(CH2)4-	C ₁₈ H ₂₆ ClN ₂ O ₄ P
262901	H	thien-2,5-diyl	C ₁₈ H ₂₀ ClN ₂ O ₄ PS
262902	3,4-(MeO)2-PhCH2	-CH2-	C ₂₄ H ₃₀ ClN ₂ O ₆ P

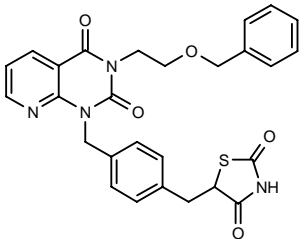
SOURCE – Otsuka.

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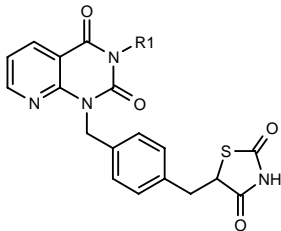
258431

3-(2-Benzoyloxyethyl)-1-[4-(2,4-dioxothiazolidin-5-ylmethyl)benzyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione



C27-H24-N4-O5-S; Mol wt: 516.57

ACTION – Agent for the treatment of diabetes and diabetic complications with aldose reductase-inhibitory activity (IC₅₀ = 1.48 μM against enzyme from rat lens), shown to decrease blood glucose levels by 59% in KK/Ta Jcl mice at 100 mg/kg p.o. b.i.d. Other compounds from this series of pyridopyrimidine derivatives include the following:



Compound	R1	Formula
263213	CH2CH2OH	C ₂₀ H ₁₈ N ₄ O ₅ S
263214	(CH2)4Ph	C ₂₈ H ₂₆ N ₄ O ₄ S
263215	CH2CH2OPh	C ₂₈ H ₂₂ N ₄ O ₅ S
263216	4- <i>i</i> -Pr-PhCH2OCH2CH2	C ₃₀ H ₃₀ N ₄ O ₅ S
263217	CH2CH2SCH2Ph	C ₂₇ H ₂₄ N ₄ O ₄ S ₂
263218	<i>i</i> -Pr	C ₂₁ H ₂₀ N ₄ O ₄ S

SOURCE – Terumo.

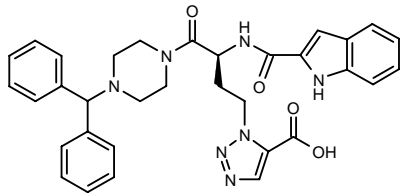
REFERENCES

1. Yonezawa, Y. and Kasukawa, H. (Terumo Corp.) *Pyridopyrimidine derivs. and medicinal compsns. containing them*. JP 97295977.

TP-1202

262474

1-[4-[4-(Diphenylmethyl)piperazin-1-yl]-3-(S)-(1*H*-indol-2-ylcarboxamido)-4-oxobutyl]-1,2,3-triazole-5-carboxylic acid



C33-H33-N7-O4; Mol wt: 591.67

ACTION – Agent for the treatment of pancreatitis, a selective CCK_A receptor antagonist (IC₅₀ = 0.037 μM) with reduced affinity for CCK_B receptors (IC₅₀ = 69 μM); the compound had an IC₅₀ value of 0.12 μM for inhibition of CCK-8-induced contractions in isolated guinea pig ileum.

SOURCE – Tobishi.

REFERENCES

1. Ogawa, M. et al. (Tobishi Pharm. Co., Ltd.) *Amino acid deriv. having anti-CKK activity*. EP 710661, JP 96119940, JP 96176144, US 5716958.

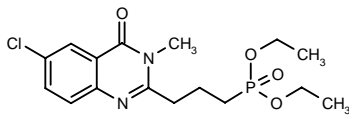
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

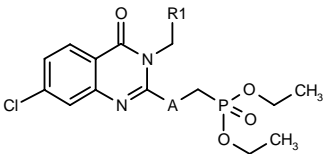
258415

3-(6-Chloro-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-propylphosphonic acid diethyl ester



C16-H22-Cl-N2-O4-P; Mol wt: 372.79

ACTION – Antidiabetic agent with potent blood glucose-lowering activity in rats (–83% at 100 mg/kg p.o. once daily for 4 consecutive days). Within this series of phosphonic acid diester derivatives, the following are also included:



Compound	R1	A	Formula
262900	H	-(CH2)4-	C ₁₈ H ₂₆ ClN ₂ O ₄ P
262901	H	thien-2,5-diyl	C ₁₈ H ₂₀ ClN ₂ O ₄ PS
262902	3,4-(MeO)2-PhCH2	-CH2-	C ₂₄ H ₃₀ ClN ₂ O ₆ P

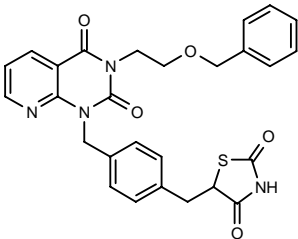
SOURCE – Otsuka.

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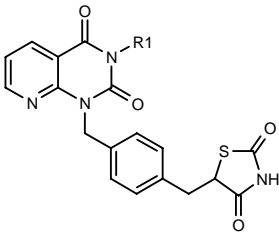
258431

3-(2-Benzoyloxyethyl)-1-[4-(2,4-dioxothiazolidin-5-ylmethyl)benzyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione



C27-H24-N4-O5-S; Mol wt: 516.57

ACTION – Agent for the treatment of diabetes and diabetic complications with aldose reductase-inhibitory activity (IC₅₀ = 1.48 μM against enzyme from rat lens), shown to decrease blood glucose levels by 59% in KK/Ta Jcl mice at 100 mg/kg p.o. b.i.d. Other compounds from this series of pyridopyrimidine derivatives include the following:



Compound	R1	Formula
263213	CH2CH2OH	C ₂₀ H ₁₈ N ₄ O ₅ S
263214	(CH2)4Ph	C ₂₈ H ₂₆ N ₄ O ₄ S
263215	CH2CH2OPh	C ₂₈ H ₂₂ N ₄ O ₅ S
263216	4-i-Pr-PhCH2OCH2CH2	C ₃₀ H ₃₀ N ₄ O ₅ S
263217	CH2CH2SCH2Ph	C ₂₇ H ₂₄ N ₄ O ₄ S ₂
263218	i-Pr	C ₂₁ H ₂₀ N ₄ O ₄ S

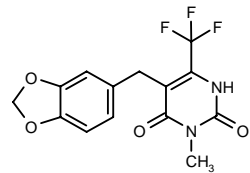
SOURCE – Terumo.

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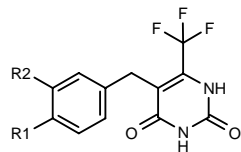
262811

5-(1,3-Benzodioxol-5-ylmethyl)-3-methyl-6-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione



C14-H11-F3-N2-O4; Mol wt: 328.25

ACTION – Hypoglycemic agent shown to decrease blood glucose levels by 45% in C57BL ob/ob mice at 30 mg/kg/day p.o. x 5 days. Within this series of trifluoromethylpyrimidine derivatives, the following are also included:



Compound	R1	R2	Formula
263092	-OCH2O-		C ₁₃ H ₉ F ₃ N ₂ O ₄
263093	-CH=CHCH=CH-		C ₁₆ H ₁₁ F ₃ N ₂ O ₂
263094	OMe	4-CF3-PhCH2NHCO	C ₂₂ H ₁₇ F ₆ N ₃ O ₄

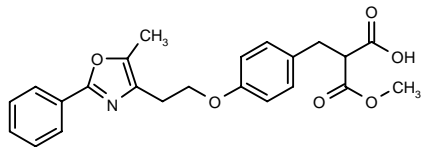
SOURCE – Kyorin.

REFERENCES

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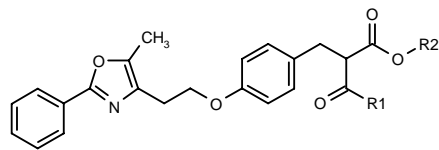
263293

2-[4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]-malonic acid monomethyl ester



C23-H23-N-O6; Mol wt: 409.44

ACTION – Hypoglycemic and hypolipidemic agent proven to enhance insulin sensitivity in 3T3-L1 cells (EC₅₀ = 0.45 nM) and to decrease blood glucose levels in KKA^y mice when administered mixed with the diet (ED₅₀ = 0.12 mg/kg/day). Other compounds from this series of propionic acid derivatives include the following:



Compound	R1	R2	Formula
264912	OH	H	C ₂₂ H ₂₁ NO ₆
264913	NHCO2Me	Me	C ₂₅ H ₂₆ N ₂ O ₇

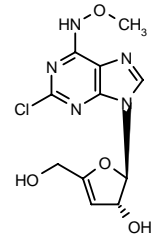
SOURCE – Japan Tobacco.

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263726

(2*R*,3*R*)-2-(2-Chloro-*N*⁶-methoxyadenin-9-yl)-5-(hydroxymethyl)-2,3-dihydrofuran-3-ol



C11-H12-Cl-N5-O4; Mol wt: 313.70

ACTION – *N*-Methoxyadenosine derivative with nano-molar affinity for the recombinant human adenosine A₃ receptor, proven to inhibit the production of tumor necrosis factor- α (TNF- α) in a rat whole blood assay with an IC₅₀ of 130 nM. Potentially useful for the treatment of disorders such as inflammation, arthritis, diabetes, autoimmune diseases, multiple sclerosis, stroke, osteoporosis, septic shock and menstrual complications, particularly type I or II diabetes.

SOURCE – Novo Nordisk.

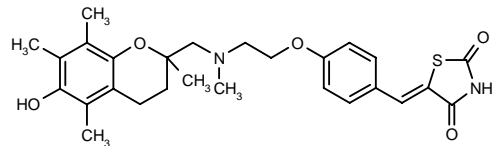
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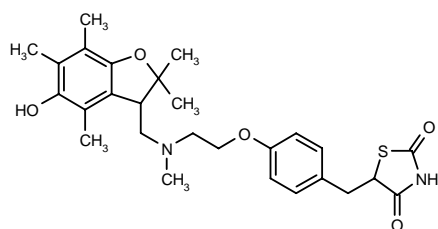
263729

(*Z*)-5-[4-[2-[*N*-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-ylmethyl)-*N*-methylamino]-ethoxy]benzylidene]-2,4-thiazolidinedione



C27-H32-N2-O5-S; Mol wt: 496.62

ACTION – Hypoglycemic and hypolipidemic agent with an antioxidant moiety. *In vivo* effects were evaluated in db/db mice, giving a 46% reduction in plasma blood glucose and a 71% reduction in plasma triglycerides at a dose of 200 mg/kg/day p.o. for 9 days, with superior potency to troglitazone. Another thiazolidinedione with an antioxidant moiety and a similar profile is:



263730: C27-H34-N2-O5-S

SOURCE – Dr. Reddy's Res. Found., Hyderabad (IN).

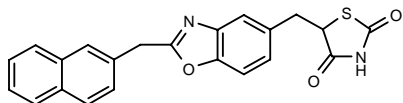
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T-174*

147445

(±)-5-(2,4-Dioxothiazolidin-5-ylmethyl)-2-(2-naphthylmethyl)benzoxazole



C22-H16-N2-O3-S; Mol wt: 388.44

ACTION – Potent hypoglycemic agent, a thiazolidinedione insulin sensitizer proven to stimulate the transcription of peroxisome proliferator-activated receptor (PPAR) γ and the adipocyte differentiation of 3T3-L1 cells. It exerted potent hypoglycemic activity in genetically diabetic and obese KKA^y mice (ED₂₅ = 0.4 mg/kg/day in the diet for 4 days); it also lowered plasma insulin, triglyceride and free fatty acid levels in this animal model. The compound was selected for further evaluation based on its high potency and low toxicity in rats when given for 14 days, but it was subsequently shown to induce cardiac hypertrophy and anemia in 90-day toxicity studies in rats and dogs.

SOURCE – Tanabe Seiyaku.

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*Identified compound **147445** (see **145745**) Drug Data Rep 1997, 19(3): 230.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

260348

Cyclo(25-29)[MeTyr¹,Ala¹⁵,D-Asp²⁵,Nie²⁷,Orn²⁹]-hGHRH-(1-29)NH₂

N-Methyl-L-tyrosyl-L-alanyl-L-aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutamyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutamyl-D-aspartyl-L-isoleucyl-L-norleucyl-L-seryl-L-ornithinamide C-25.4-N-29.6-lactam

C151-H248-N42-O41; Mol wt: 3307.88

ACTION – A cyclic analog of the active fragment of human growth hormone-releasing hormone (hGHRH) with a potency *in vitro* 17 times higher than hGHRH(1-40)-OH in the rat pituitary cell culture assay.

SOURCE – The Salk Inst., La Jolla, CA (US).

REFERENCES

- Cervini, L.A. et al. *Human growth hormone-releasing hormone hGHRH(1-29)-NH₂: Systematic structure-activity relationship studies.* J Med Chem 1998, 41(5): 717.

TREATMENT OF MALE SEXUAL DYSFUNCTION

SILDENAFIL⁺ CITRATE

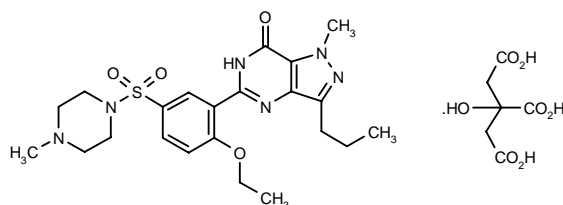
Prop INN; BAN; USAN

184491

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one citrate

UK-92480 (as free base)

UK-92480-10



C22-H30-N6-O4-S.C6-H8-O7; Mol wt: 666.70

ACTION – Selective, orally active phosphodiesterase type V (PDE V) inhibitor that results in smooth muscle relaxation in the corpus cavernosum and increased blood flow into the penis.

INDICATION – Treatment of male erectile dysfunction.

PRESENTATION – Tablets, equiv. to 25, 50 and 100 mg of sildenafil.

PROPRIETARY NAME – *Viagra* (US).

SOURCE – Pfizer.

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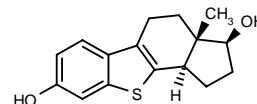
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*Drug Data Rep 1995, 17(11): 1019.

TREATMENT OF GYNECOLOGICAL DISORDERS

262083

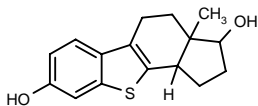
(3 β ,3 α \beta,10 β α)-3a-Methyl-2,3,3a,4,5,10b-hexahydro-1H-benz[b]indeno[5,4-d]thiophene-3,8-diol



C16-H18-O2-S; Mol wt: 274.38

ACTION – Selective estrogen receptor modulator (SERM) with potential in the treatment of estrogen-related disorders including postmenopausal syndrome, osteoporosis, hyperlipidemia, estrogen-dependent breast cancer, uterine fibrosis, endometriosis and restenosis. In competition binding studies using [³H]-17 β -estradiol, compound displayed high affinity for estrogen receptors from human breast cancer MCF-7 cell preparations, with a relative binding affinity (IC₅₀ 17 β -estradiol/IC₅₀ test compound) of 16. In ovariectomized rats, it reduced serum cholesterol levels (30.7% at 10.0 mg/kg/day p.o.) with little

stimulatory effect on the uterus compared to 17 α -ethinylestradiol and no stimulatory effect on eosinophil infiltration into the uterus. Within this series of 8-substituted B-nor-6-thiaquinelin derivatives, the following are also specifically claimed:



Compound	Isomer	Formula
263382	3 β ,3a β ,10b β	C ₁₆ H ₁₈ O ₂ S
263383	3 α ,3a β ,10b α	C ₁₆ H ₁₈ O ₂ S
263384	3 α ,3a α ,10b α	C ₁₆ H ₁₈ O ₂ S
263385	3 α ,3a α ,10b β	C ₁₆ H ₁₈ O ₂ S

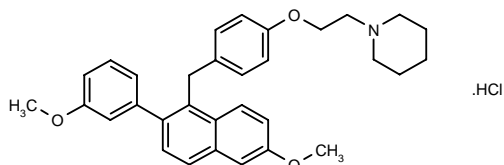
SOURCE – Lilly.

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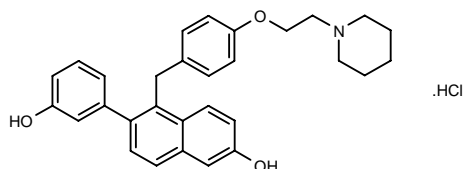
262100

1-[2-[4-[6-Methoxy-2-(3-methoxyphenyl)naphthalen-1-ylmethyl]phenoxy]ethyl]piperidine hydrochloride



C32-H35-N-O3.HCl; Mol wt: 518.09

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disease related to hyperlipidemia and estrogen-dependent cancer, as well as uterine fibroid disease, endometriosis and restenosis. Compound was tested in a model of postmenopausal hyperlipidemia in ovariectomized rats, where it reduced serum cholesterol compared to ovariectomized animals but increased uterine weight to a lesser extent than 17 α -ethinylestradiol at doses of 0.1-10 mg/kg p.o. It also exhibited anti-proliferative activity against human breast adenocarcinoma MCF-7 cells, with an IC₅₀ value of 0.1 nM. Another representative compound within this series of naphthalenes is:



262844: C30-H31-N-O3.HCl

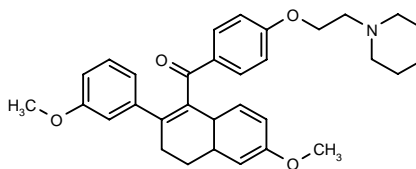
SOURCE – Lilly.

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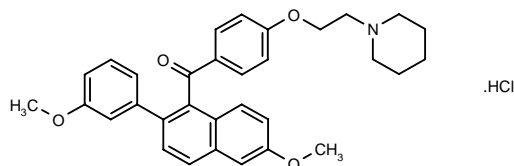
262101

1-[6-Methoxy-2-(3-methoxyphenyl)-3,4-dihydronaphthalen-1-yl]-1-[4-[2-(1-piperidinyloxy)]phenyl]methanone



C32-H37-N-O4; Mol wt: 499.65

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disease related to hyperlipidemia and estrogen-dependent cancer, as well as uterine fibroid disease, endometriosis and restenosis. Compound was tested in a model of postmenopausal hyperlipidemia in ovariectomized rats, where it reduced serum cholesterol compared to ovariectomized animals but increased uterine weight to a lesser extent than 17 α -ethinylestradiol at doses of 0.01-10 mg/kg p.o. Another representative compound within this series of dihydronaphthalenes and naphthalenes is:



262845: C32-H33-N-O4.HCl

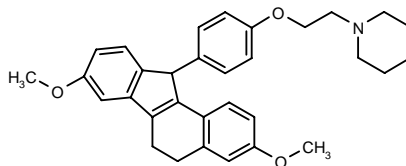
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly & Co.) *Dihydronaphthalene and naphthalene cpds., intermediates, formulations, and methods*. EP 826680, JP 98087577.

264656

1-[2-[4-(3,8-Dimethoxy-6,11-dihydro-5H-benzo[a]fluoren-11-yl)phenoxy]ethyl]piperidine



C32-H35-N-O3; Mol wt: 481.63

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disease related to hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis, reported to be devoid of the side effects associated with estrogen therapy.

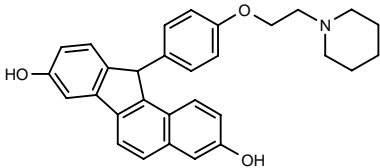
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly & Co.) *Dihydrobenzofluorene cpds., intermediates, compsns., and methods*. EP 832880.

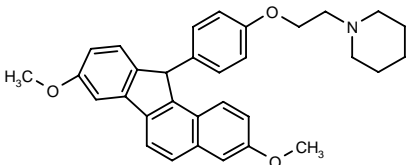
264657

11-[4-[2-(1-Piperidinyloxy)phenyl]-11H-benzo[a]-fluorene-3,8-diol



C30-H29-N-O3; Mol wt: 451.56

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders related to hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 0.1, 1 and 10 mg/kg/day p.o. while it did not induce any increase in uterine weight, contrary to 17α-ethinylestradiol at 0.1 mg/kg/day p.o.; at these doses, compound was shown to produce much lower increases in uterine eosinophil infiltration than 17α-ethinylestradiol. In addition, it was shown to prevent bone loss in ovariectomized rats at 0.1 and 1.0 mg/kg/day and inhibited the growth of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 0.11 nM. Another compound from this series of benzofluorene derivatives is:



264976: C32-H33-N-O3

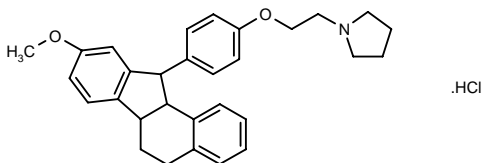
SOURCE – Lilly.

REFERENCES

1. Crowell, T.A. et al. (Eli Lilly & Co.) *Benzofluorene cpds., intermediates, compsns., and methods*. EP 832881, JP 98130211.

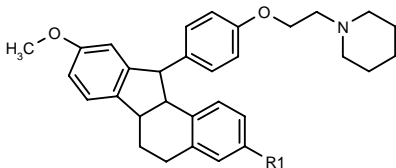
264659

1-[2-[4-(9-Methoxy-6,6a,11,11a-hexahydro-5H-benzo[a]-fluoren-11-yl)phenoxy]ethyl]pyrrolidine



C30-H33-N-O2.HCl; Mol wt: 476.06

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders related to hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis. A representative compound from a series of tetrahydrobenzo[a]fluorene derivatives, wherein the following are also included:



Compound	R1	Formula
264932	OMe	C ₃₂ H ₃₇ NO ₃
264933	H	C ₃₁ H ₃₅ NO ₂

SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. and Cullinan, G.J. (Eli Lilly & Co.) *Tetrahydrobenzo(a)fluorene cpds. and methods of use*. EP 832883.

TREATMENT OF FEMALE INFERTILITY

RECOMBINANT HUMAN LUTEINIZING HORMONE

230542

r-hLH
LHadi®

ACTION – Recombinant human luteinizing hormone (hLH) potentially useful for hormone-related therapy supporting human follicle-stimulating hormone (FSH)-induced follicular development in hypogonadotropic hypogonadal women. Pharmacokinetics in healthy women are linear to dose and comparable to those of human urinary LH, and it was well tolerated at doses of up to 40,000 IU i.v.

SOURCE – Ares Serono.

REFERENCES

1. Baird, D.T. et al. *Recent development in gonadotrophins for clinical therapy*. J Endocrinol 1996, 148(Suppl.): Abst S38.

2. le Cotonnec, J.-Y. et al. *Pharmacokinetic and pharmacodynamic interactions between recombinant human luteinizing hormone and recombinant human follicle stimulating hormone*. Fertil Steril 1998, 69(2): 201.

3. le Cotonnec, J.-Y. et al. *Clinical pharmacology of recombinant human luteinizing hormone: Part I. Pharmacokinetics after intravenous administration to healthy female volunteers and comparison with urinary human luteinizing hormone*. Fertil Steril 1998, 69(2): 189.

4. le Cotonnec, J.-Y. et al. *Clinical pharmacology of recombinant human luteinizing hormone: Part II. Bioavailability of recombinant human luteinizing hormone assessed with an immunoassay and an in vitro bioassay*. Fertil Steril 1998, 69(2): 195.

5. *In development: Biotechnology medicines*. Pharmaceutical Research and Manufacturers of America 1995, March.

6. *The Ares Serono Group and Organon conclude settlement agreement*. The Ares Serono Group Press Release 1995, May 23.

7. Ares Serono Group Annual Report 1994.

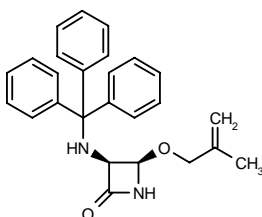
8. Ares Serono Group Annual Report 1997.

DERMATOLOGIC DRUGS

TOPICAL ANTIINFLAMMATORY
DRUGS

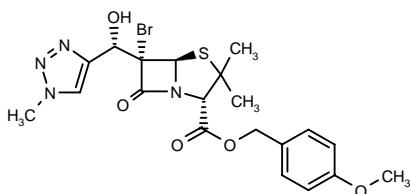
SB-216754

262717

(3*S*,4*R*)-4-(2-Methyl-2-propenyloxy)-3-(triphenylmethylamino)azetidin-2-one

C26-H26-N2-O2; Mol wt: 398.50

ACTION – Specific, irreversible and time-dependent inhibitor of coenzyme A-independent transacylase (CoA-IT) activity ($IC_{50} = 20 \mu M$ with 10-min preincubation and $6 \mu M$ with 80-min preincubation using U937 cell microsomes). The compound inhibits the production of PAF in stimulated human neutrophils ($IC_{50} = 5 \mu M$) and the production of eicosanoids (LTC_4 and PGE_2) in human monocytes at concentrations of 3-30 μM . In an *in vivo* model of phorbol ester-induced ear inflammation in mice, the compound administered topically reduced both edema ($ED_{50} = 0.49$ mg/ear at 4 h) and myeloperoxidase activity ($ED_{50} = 0.48$ mg/ear), and it was also active in a chronic inflammatory model (0.75 mg/ear b.i.d. for 3 days). Another β -lactam is:



SB-212047 [262718]: C20-H23-Br-N4-O5-S

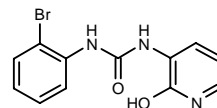
SOURCE – SmithKline Beecham.

REFERENCES

1. Winkler, J.D. et al. β -Lactams SB 212047 and SB 216754 are irreversible, time-dependent inhibitors of coenzyme A-independent transacylase. *Mol Pharmacol* 1998, 53(2): 322.

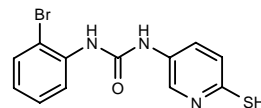
ANTIPSORIATICS

260155

N-(2-Bromophenyl)-*N'*-(2-hydroxy-3-pyridyl)urea

C12-H10-Br-N3-O2; Mol wt: 308.13

ACTION – IL-8 receptor antagonist with potential in the treatment of a broad range of diseases mediated by IL-8 or other chemokines, reported to inhibit the binding of chemokines such as IL-8, $GRO\alpha$, $GRO\beta$, $GRO\gamma$, NAP-2 or ENA-78, particularly IL-8, to the IL-8 α or β receptor (now known as CXCR1 and CXCR2 receptor, respectively). Potentially useful for the treatment of psoriasis, arthritis, asthma, inflammatory bowel disease, stroke, septic shock, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft-versus-host disease, Alzheimer's disease and angiogenesis. Another related compound is:



263014: C12-H10-Br-N3-O-S

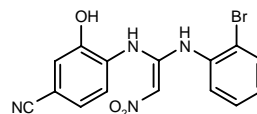
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9749400.

262904

4-[1-(2-Bromophenylamino)-2-nitrovinylamino]-3-hydroxybenzonitrile



C15-H11-Br-N4-O3; Mol wt: 375.18

ACTION – IL-8 receptor antagonist for the treatment of chemokine-mediated diseases such as psoriasis, dermatitis, asthma, adult respiratory distress syndrome, arthritis and other inflammatory disorders. The compound is reported to be able to inhibit the binding of a chemokine such as IL-8, $GRO\alpha$, $GRO\beta$, $GRO\gamma$, ENA-78 or NAP-2, particularly IL-8, to the IL-8 type I or type II receptor (now known as CXCR1 and CXCR2 receptors, respectively).

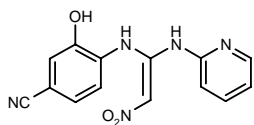
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Gleason, J.G. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9805317.

262906

3-Hydroxy-4-[2-nitro-1-(2-pyridylamino)vinylamino]-benzonitrile



C₁₄H₁₁N₅O₃; Mol wt: 297.27

ACTION – IL-8 receptor antagonist for the treatment of chemokine-mediated diseases such as psoriasis, dermatitis, asthma, adult respiratory distress syndrome, arthritis and other inflammatory diseases. The compound is reported to be able to inhibit the binding of a chemokine such as IL-8, GRO α , GRO β , GRO γ , ENA-78 or NAP-2, particularly IL-8, to the IL-8 type I or type II receptor (now known as CXCR1 and CXCR2 receptors, respectively).

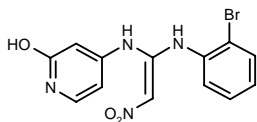
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Gleason, J.G. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9805328.

262907

N-(2-Bromophenyl)-*N'*-(2-hydroxy-4-pyridyl)-2-nitroethylene-1,1-diamine



C₁₃H₁₁BrN₄O₃; Mol wt: 351.16

ACTION – IL-8 receptor antagonist for the treatment of chemokine-mediated diseases such as psoriasis, dermatitis, asthma, adult respiratory distress syndrome, arthritis and other inflammatory disorders. The compound is reported to be able to inhibit the binding of a chemokine such as IL-8, GRO α , GRO β , GRO γ , ENA-78 or NAP-2, particularly IL-8, to the IL-8 type I or type II receptor (now known as CXCR1 and CXCR2 receptors, respectively).

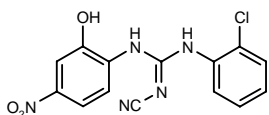
SOURCE – SmithKline Beecham.

REFERENCES

1. Widdowson, K.L. and Gleason, J.G. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9805329.

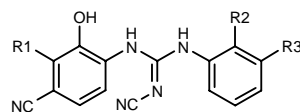
263239

1-(2-Chlorophenyl)-2-cyano-3-(2-hydroxy-4-nitrophenyl)-guanidine



C₁₄H₁₀ClN₅O₃; Mol wt: 331.72

ACTION – IL-8 receptor antagonist for the treatment of chemokine-mediated disorders including psoriasis, atopic dermatitis, asthma, arthritis, ulcerative colitis and endotoxic shock. It is reported to inhibit the binding of chemokines such as IL-8, GRO α , GRO β , GRO γ , ENA-78 or NAP-2 to the IL-8 α or β receptor (now known as CXCR1 and CXCR2 receptors, respectively). Other specifically claimed guanidine-containing compounds include the following:



Compound	R1	R2	R3	Formula
263542	H	Br	H	C ₁₅ H ₁₀ BrN ₅ O
263543	H	H	H	C ₁₅ H ₁₁ N ₅ O
263544	H	Cl	Cl	C ₁₅ H ₉ Cl ₂ N ₅ O
263545	Pr	Br	H	C ₁₈ H ₁₆ BrN ₅ O
263546	Pr	Cl	Cl	C ₁₈ H ₁₅ Cl ₂ N ₅ O
263547	Pr	Cl	H	C ₁₈ H ₁₆ ClN ₅ O
263548	i-Bu	Br	H	C ₁₉ H ₁₈ BrN ₅ O
263549	Br	Br	H	C ₁₅ H ₉ Br ₂ N ₅ O
263550	Br	-OCH ₂ O-		C ₁₆ H ₁₀ BrN ₅ O ₃
263551	CO ₂ Me	Br	H	C ₁₇ H ₁₂ BrN ₅ O ₃

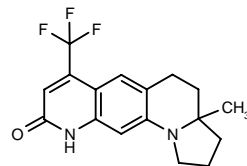
SOURCE – SmithKline Beecham.

REFERENCES

1. Bryan, D.L. et al. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. WO 9806397.

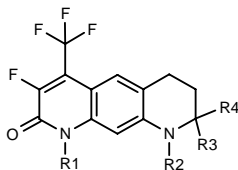
ACNE THERAPY**260199**

3a-Methyl-7-(trifluoromethyl)-1,2,3,3a,4,5,9,10-octa-hydroindolizino[6,7-*g*]quinolin-9-one



C₇H₁₇F₃N₂O; Mol wt: 202.22

ACTION – Nonsteroidal androgen receptor modulator for the treatment of acne, hirsutism, male pattern baldness, prostatic hyperplasia and hormone-dependent cancers. It gave a K_i value of 169 nM in an androgen receptor binding assay using tritiated dihydrotestosterone as the ligand in COS-1 cells. Antiandrogenic activity was determined by measuring the inhibition of mouse renal ornithine decarboxylase activity, with about 30% inhibition at a dose of 1 mg/mouse p.o. Other related compounds include the following:



Compound	R1	R2	R3=R4	Formula
262711	H	-(CH2)3-		C ₁₇ H ₁₆ F ₄ N ₂ O
262712	Me	H	Me	C ₁₆ H ₁₆ F ₄ N ₂ O
262713	H	H	Et	C ₁₇ H ₁₈ F ₄ N ₂ O

SOURCE – Ligand.

REFERENCES

1. Edwards, J.P. et al. (Ligand Pharm., Inc.) *Androgen receptor modulator cpds. and methods.* WO 9749709.

WOUND-HEALING AGENTS

BECAPLERMIN+

Prop INN; BAN; USAN

198489

Recombinant human platelet-derived growth factor (rhPDGF-BB, homodimer) produced from genetically engineered *Saccharomyces cerevisiae* cells into which the gene for the B-chain of PDGF has been inserted

rhPDGF-BB
RWJ-60235

ACTION – Recombinant human platelet-derived growth factor (rhPDGF-BB) that mimics the naturally occurring protein and stimulates the migration of cells to the ulcer site, thereby promoting the growth of new tissue.

INDICATION – Adjunct in the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply.

PRESENTATION – Gel, 0.01%.

PROPRIETARY NAME – Regranex (US).

SOURCES – Chiron; developed by R.W. Johnson and marketed by Ortho-McNeil.

RECENT REFERENCES

1. Wieman, T.J. et al. *Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: A phase III randomized placebo-controlled double-blind study.* Diabetes Care 1998, 21(5): 822.
2. *Becaplermin launch.* Ortho-McNeil Pharmaceutical Press Release 1998, April 24.
3. *FDA clears Regranex® (becaplermin) gel 0.01% for diabetic foot ulcers.* Johnson & Johnson Press Release 1997, December 17.
4. *FDA clears Regranex® (becaplermin) gel 0.01% for diabetic foot ulcers. - New biologic stimulates the body to grow new tissue.* Ortho-McNeil Pharmaceutical Press Release 1997, December 16.
5. *First biologic approved for treatment of diabetic foot ulcers.* Prous Science Daily Essentials December 18, 1997.

6. *First launch for topical biologic that helps heal diabetic foot ulcers.* Prous Science Daily Essentials April 20, 1998.
7. *Promotion agreement established for wound-healing drugs.* Prous Science Daily Essentials March 6, 1998.
8. *Regranex® (becaplermin) gel 0.01% for diabetic foot ulcers now available to patients. - New biologic stimulates the body to grow new tissue.* Ortho-McNeil Pharmaceutical Press Release 1998, April 16.
9. *Regranex recommended for approval by FDA advisory committee.* Prous Science Daily Essentials July 16, 1997.

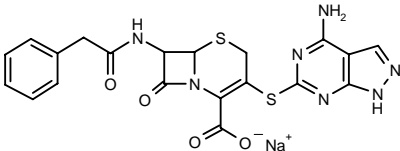
*Drug Data Rep 1997, 19(2): 145.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

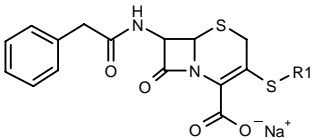
261856

3-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylsulfanyl)-7-(2-phenylacetamido)-3-cephem-4-carboxylic acid sodium salt



C20-H16-N7-Na-O4-S2; Mol wt: 505.50

ACTION – Cephem antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P (MIC = 0.2 µg/ml), and also methicillin-resistant *S. aureus* strains such as strain F-597 (MIC = 1.56 µg/ml). Within this series of novel cephalosporin derivatives, the following are also included:

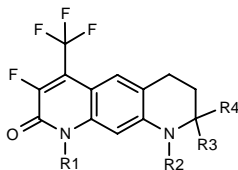


Compound	R1	Formula
262757	4-NH2-2-pyrimidinyl	C ₁₉ H ₁₆ N ₆ NaO ₄ S ₂
262758	4-NH2-6-OH-2-pyrimidinyl	C ₁₉ H ₁₆ N ₆ NaO ₅ S ₂
262759	6-NH2-9H-purin-2-yl	C ₂₀ H ₁₆ N ₇ NaO ₄ S ₂
262760	2-NH2-9H-purin-6-yl	C ₂₀ H ₁₆ N ₇ NaO ₄ S ₂
262761	4-NH2-2-quinazoliny	C ₂₃ H ₁₈ N ₆ NaO ₄ S ₂
262762	2-NH2-4-pteridinyl	C ₂₁ H ₁₆ N ₇ NaO ₄ S ₂

SOURCE – Toyama.

REFERENCES

1. Takagi, H. et al. (Toyama Chem. Co., Ltd.) *Novel cephalosporin derivs. and their salts.* JP 98036375.



Compound	R1	R2	R3=R4	Formula
262711	H	-(CH2)3-		C ₁₇ H ₁₆ F ₄ N ₂ O
262712	Me	H	Me	C ₁₆ H ₁₆ F ₄ N ₂ O
262713	H	H	Et	C ₁₇ H ₁₈ F ₄ N ₂ O

SOURCE – Ligand.

REFERENCES

1. Edwards, J.P. et al. (Ligand Pharm., Inc.) *Androgen receptor modulator cpds. and methods.* WO 9749709.

WOUND-HEALING AGENTS

BECAPLERMIN+

Prop INN; BAN; USAN

198489

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rhPDGF-BB
RWJ-60235

ACTION – Recombinant human platelet-derived growth factor (rhPDGF-BB) that mimics the naturally occurring protein and stimulates the migration of cells to the ulcer site, thereby promoting the growth of new tissue.

INDICATION – Adjunct in the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply.

PRESENTATION – Gel, 0.01%.

PROPRIETARY NAME – Regranex (US).

SOURCES – Chiron; developed by R.W. Johnson and marketed by Ortho-McNeil.

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1. Wieman, T.J. et al. *Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: A phase III randomized placebo-controlled double-blind study.* Diabetes Care 1998, 21(5): 822.
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9. *Regranex recommended for approval by FDA advisory committee.* Prous Science Daily Essentials July 16, 1997.

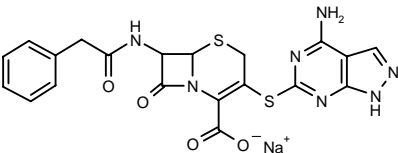
*Drug Data Rep 1997, 19(2): 145.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

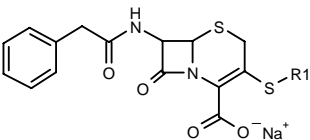
261856

3-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylsulfanyl)-7-(2-phenylacetamido)-3-cephem-4-carboxylic acid sodium salt



C20-H16-N7-Na-O4-S2; Mol wt: 505.50

ACTION – Cephem antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P (MIC = 0.2 µg/ml), and also methicillin-resistant *S. aureus* strains such as strain F-597 (MIC = 1.56 µg/ml). Within this series of novel cephalosporin derivatives, the following are also included:



Compound	R1	Formula
262757	4-NH2-2-pyrimidinyl	C ₁₉ H ₁₆ N ₆ NaO ₅ S ₂
262758	4-NH2-6-OH-2-pyrimidinyl	C ₁₉ H ₁₆ N ₆ NaO ₅ S ₂
262759	6-NH2-9H-purin-2-yl	C ₂₀ H ₁₆ N ₇ NaO ₄ S ₂
262760	2-NH2-9H-purin-6-yl	C ₂₀ H ₁₆ N ₇ NaO ₄ S ₂
262761	4-NH2-2-quinazoliny	C ₂₃ H ₁₈ N ₆ NaO ₄ S ₂
262762	2-NH2-4-pteridinyl	C ₂₁ H ₁₆ N ₇ NaO ₄ S ₂

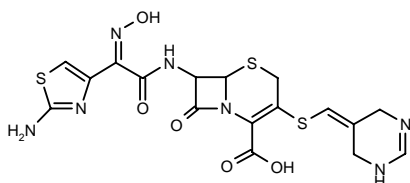
SOURCE – Toyama.

REFERENCES

1. Takagi, H. et al. (Toyama Chem. Co., Ltd.) *Novel cephalosporin derivs. and their salts.* JP 98036375.

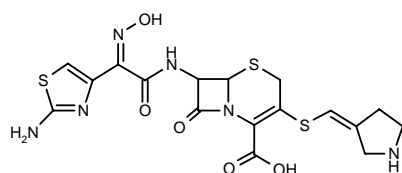
261879

7-[2-(2-Aminothiazol-4-yl)-2(Z)-(hydroxyimino)-acetamido]-3-(1,4,5,6-tetrahydropyrimidin-5-ylidene-methylsulfanyl)-3-cephem-4-carboxylic acid



C17-H17-N7-O5-S3; Mol wt: 495.55

ACTION – Cephalosporin antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* FDA 209P (MIC = 0.1 µg/ml) and *Escherichia coli* NIHJ (MIC = 0.1 µg/ml). Another representative compound within this series of cephalosporins is:



262756: C17-H18-N6-O5-S3

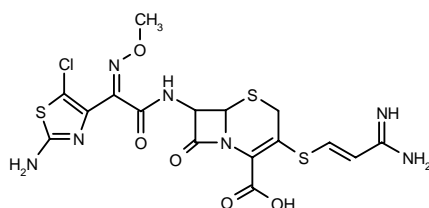
SOURCE – Toyama.

REFERENCES

1. Takagi, H. et al. (Toyama Chem. Co., Ltd.) *Novel cephalosporins or their salts*. JP 98045765.

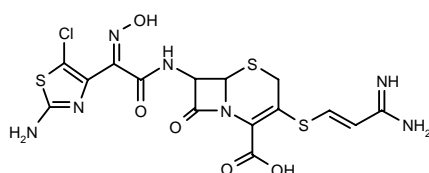
261880

3-[2(E)-Amidinovinylsulfanyl]-7-[2-(2-amino-5-chloro-thiazol-4-yl)-2(Z)-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid



C16-H16-Cl-N7-O5-S3; Mol wt: 517.98

ACTION – Cephalosporin antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P (MIC = 0.1 µg/ml), *Escherichia coli* NIHJ (MIC = 0.05 µg/ml or less) and methicillin-resistant *S. aureus* strains such as F-597 (MIC = 0.78 µg/ml). Another representative compound within this series of cephalosporin derivatives is:



262763: C15-H14-Cl-N7-O5-S3

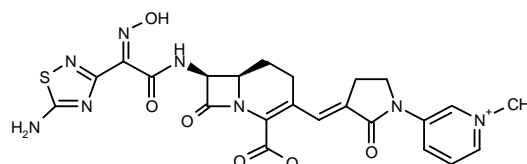
SOURCE – Toyama.

REFERENCES

1. Takagi, H. et al. (Toyama Chem. Co., Ltd.) *Novel cephalosporin derivs. and their salts*. JP 98045766.

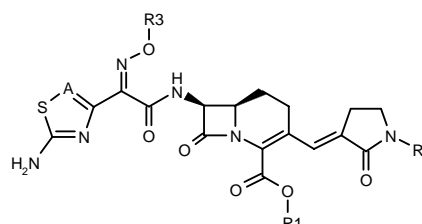
262124

(6R,7S)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(Z)-(hydroxyimino)acetamido]-3-[1-(methylpyridinium-3-yl)-2-oxopyrrolidin-3(E)-ylidenemethyl]-1-carba-3-cephem-4-carboxylate



C23-H22-N8-O6-S; Mol wt: 538.54

ACTION – Carbacephem antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* 6538 (MIC = 0.5 µg/ml), *Streptococcus pneumoniae* 907 (MIC = 0.06 µg/ml or less) and *Escherichia coli* 25922 (MIC = 0.06 µg/ml); it also has notable activity against methicillin-resistant staphylococci, e.g., *S. aureus* 743 (MIC = 8 µg/ml), and against *Pseudomonas aeruginosa* ATCC 27853 (MIC = 8 µg/ml). Other representative compounds within this series of 1-carba-(dethia)-cephalosporin derivatives include the following:



Compound	R1	R2	R3	A	Formula
262893	Na	CH ₂ CF ₃	H	CH	C ₂₀ H ₁₈ F ₃ N ₆ NaO ₆ S
262894	Na	4-OH-Ph	H	CH	C ₂₄ H ₂₁ N ₆ NaO ₇ S
262895	negative charge	1-Me-3-Pyr	H	CH	C ₂₄ H ₂₃ N ₇ O ₆ S
262896	negative charge	1-Me-3-Pyr	cyclopentyl	N	C ₂₈ H ₃₀ N ₈ O ₆ S
262897	negative charge	1-Me-3-Pyr	CH ₂ CO ₂ Na	CH	C ₂₆ H ₂₄ N ₇ NaO ₆ S
262898	negative charge	1-Me-4-Pyr	cyclopentyl	CH	C ₂₉ H ₃₁ N ₇ O ₆ S

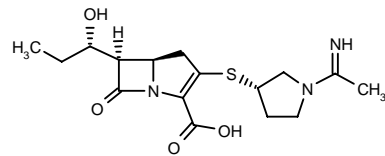
SOURCE – Roche.

REFERENCES

1. Angehrn, P. et al. (F. Hoffmann-La Roche AG) *1-Carba-(dethia)-cephalosporin derivs*. EP 831093, JP 98101670.

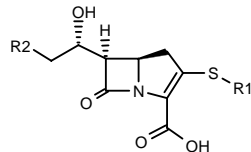
262105

(5*R*,6*R*)-2-[1-Acetimidoylpyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*S*)-hydroxypropyl]-1-carba-2-penem-3-carboxylic acid



C16-H23-N3-O4-S; Mol wt: 353.44

ACTION – Carbapenem antibiotic active *in vitro* against methicillin-resistant *Staphylococcus aureus*, e.g., strains 31 and 33 (MICs = 6.25 µg/ml) which are also resistant to imipenem, and *Staphylococcus aureus* 209P JC-1 (MIC = 0.05 µg/ml) and *Escherichia coli* NIHJ JC-2 (MIC = 0.2 µg/ml). Other representative compounds within this series of carbapenem derivatives include the following:



Compound	R1	R2	Formula
262861	Ph	Me	C ₁₆ H ₁₇ NO ₄ S
262862	3(<i>S</i>)-pyrrolidinyl	Me	C ₁₄ H ₂₀ N ₂ O ₄ S
262863	1-allyl-3(<i>S</i>)-pyrrolidinyl	Me	C ₁₇ H ₂₄ N ₂ O ₄ S
262864	3(<i>S</i>)-pyrrolidinyl	H	C ₁₃ H ₁₈ N ₂ O ₄ S
262865	1-allyl-3(<i>S</i>)-pyrrolidinyl	H	C ₁₆ H ₂₂ N ₂ O ₄ S
262866	1-allyl-5(<i>S</i>)-[CON(Me) ₂]-3(<i>S</i>)-pyrrolidinyl	Me	C ₂₀ H ₂₉ N ₃ O ₅ S
262867	1-(PhCOCH ₂)-3(<i>S</i>)-pyrrolidinyl	Me	C ₂₂ H ₂₆ N ₂ O ₅ S
262868	4-Pip	Me	C ₁₅ H ₂₂ N ₂ O ₄ S

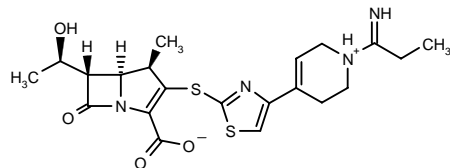
SOURCE – Suntory.

REFERENCES

1. Ishiguro, M. et al. (Suntory, Ltd.) *Carbapenem derivs. and antimicrobial agents comprising the same*. EP 826687, JP 98059970.

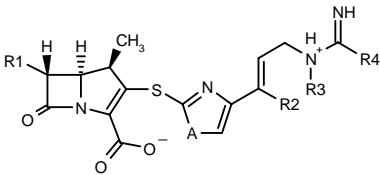
262826

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[4-[1-(1-iminopropyl)-1,2,3,6-tetrahydropyridin-4-yl]thiazol-2-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid inner salt



C21-H26-N4-O4-S2; Mol wt: 462.58

ACTION – Carbapenem antibacterial agent active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other compounds from this series of carbapenems include the following:



Compound	R1	R2	R3	R4	A	Formula
263069	(<i>R</i>)-CH(OH)Me	-(CH ₂) ₂ -		CH ₂ CH ₂ OH	S	C ₂₁ H ₂₆ N ₄ O ₅ S ₂
263070	CH ₂ OH	-(CH ₂) ₂ -		H	S	C ₁₈ H ₂₀ N ₄ O ₄ S ₂
263071	(<i>R</i>)-CH(OH)Me	-(CH ₂) ₂ -		Me	O	C ₂₀ H ₂₄ N ₄ O ₅ S
263072	(<i>R</i>)-CH(OH)Me	-(CH ₂) ₃ -		H	S	C ₂₀ H ₂₄ N ₄ O ₄ S ₂

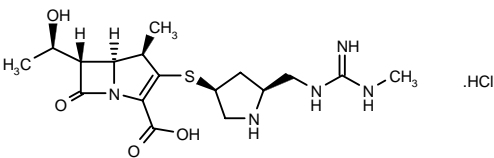
SOURCE – Sumitomo.

REFERENCES

1. Sunagawa, J. et al. (Sumitomo Pharm. Co., Ltd.) *Novel β-lactam cpds. and their preparation method*. JP 98077285, WO 9809965.

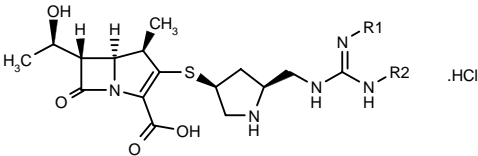
262832

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-(N'-methylguanidinomethyl)pyrrolidin-3(*S*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid hydrochloride



C17-H27-N5-O4-S.HCl; Mol wt: 433.95

ACTION – Carbapenem antibacterial agent with more potent *in vitro* activity than imipenem against several Gram-negative bacteria such as *Escherichia coli* NIHJ JC-2 (MIC = 0.025 µg/ml vs. 0.1 µg/ml), *Haemophilus influenzae* NN400 (MIC = 0.1 µg/ml vs. 0.78 µg/ml), *Pseudomonas aeruginosa* P9 (MIC = 0.39 µg/ml vs. 0.78 µg/ml) and *P. aeruginosa* NC-5 (MIC = 3.13 µg/ml vs. 25 µg/ml). Within this series of carbapenems, the following are also included:



Compound	R1	R2	Formula
263561	H	cyclopropyl	C ₁₉ H ₂₉ N ₅ O ₄ S.HCl
263562	H	i-Pr	C ₁₉ H ₃₁ N ₅ O ₄ S.HCl
263563		-(CH ₂) ₂ -	C ₁₈ H ₂₇ N ₅ O ₄ S.HCl

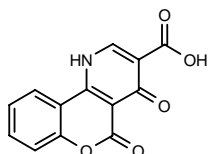
SOURCE – Takeda.

REFERENCES

1. Miwa, T. et al. (Takeda Chem. Ind., Ltd.) *Carbapenem cpds., their preparation method and agents*. JP 98081686.

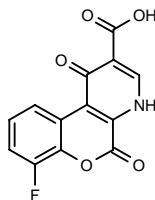
**MISCELLANEOUS
ANTIBACTERIAL DRUGS****260884**

4,5-Dioxo-4,5-dihydro-1*H*-1-benzopyrano[4,3-*b*]pyridine-3-carboxylic acid

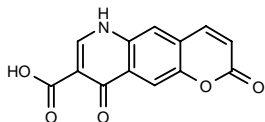


C13-H7-N-O5; Mol wt: 257.20

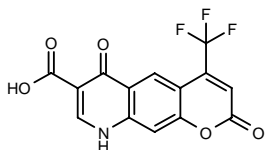
ACTION – Antibacterial agent reported to be active against *Escherichia coli* Lac+ 6131 and β -hemolytic *Streptococcus* A J-21. A representative compound from a series of coumarin-quinolonecarboxylic acids, wherein the following are also included:



263386: C13-H6-F-N-O-5



263387: C13-H7-N-O5



263388: C14-H6-F3-N-O5

Some compounds within the invention are reported to possess antineoplastic activity.

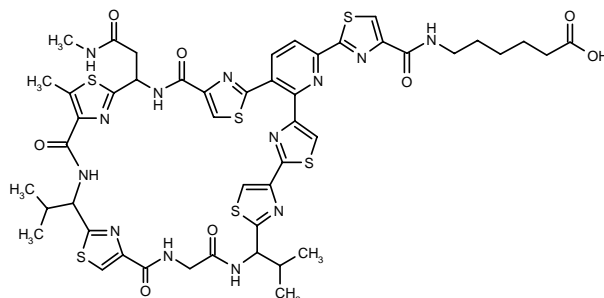
SOURCE – Pliva.

REFERENCES

1. Trkovnik, M. et al. (Pliva Pharm., Chem., Food & Cosmetic Ind., Inc.) *Novel coumarin quinolone carboxylic acids and processes for the preparation thereof*. EP 820998, JP 98087668.

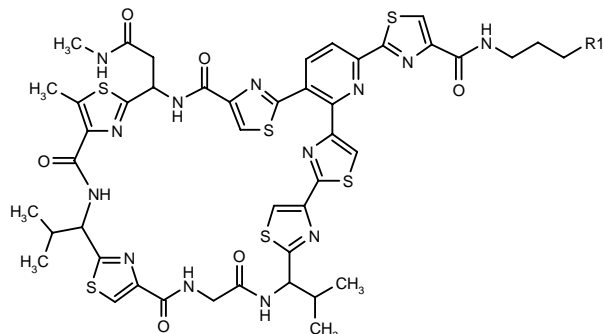
262094

6-[2-[18,28-Diisopropyl-14-methyl-11-(*N*-methyl-carbamoylmethyl)-9,16,23,26-tetraoxo-10,11,17,18,23,24,25,26,27,28-decahydro-9*H*,16*H*-8,5:15,12:22,19:32,29:36,33-pentanitrilo-5*H*,29*H*,33*H*-pyrido[3,2-*a*]₁]-[1,11,18,25,31,4,7,14,21]pentathiatetraazacyclotetratria-contin-2-yl]thiazol-4-ylcarboxamido]hexanoic acid



C48-H51-N13-O8-S6; Mol wt: 1130.37

ACTION – Water-soluble antibacterial agent found to exhibit excellent antibacterial activity against methicillin-resistant *Staphylococcus aureus* strains No. 5 and No. 17 (MIC = 0.2 μ g/ml) and other Gram-positive bacteria such as *Staphylococcus aureus* Smith (MIC = 0.1 μ g/ml) and *Micrococcus luteus* PIC 1001 (MIC = 0.1 μ g/ml). Other specifically claimed amide derivatives of amythiamicin include the following:



Compound	R1	Formula
262869	NH2	C ₄₅ H ₄₈ N ₁₄ O ₆ S ₆
262870	4-Cl-PhCH2CH2NH(CH2)3N(Me)	C ₅₇ H ₆₄ ClN ₁₅ O ₆ S ₆

SOURCE – Microbial Chem. Res. Found., Tokyo (JP).

REFERENCES

1. Muraoka, Y. et al. (Microbial Chem. Res. Found.) *An amide deriv. of amythiamicin*. EP 825194.

263286

Alanyl-glycyl-arginyl-glycyl-lysyl-glutaminyl-glycyl-glycyl-lysyl-valyl-arginyl-alanyl-lysyl-alanyl-lysyl-threonyl-arginyl-seryl-seryl-arginyl-alanyl-glycyl-leucyl-glutaminy-phenylalanyl-prolyl-valyl-glycyl-arginyl-valyl-histidyl-histidyl-leucyl-leucyl-leucyl-leucyl-lysyl-glycyl-asparaginy-tyrosine

C190-H323-N67-O48; Mol wt: 4314.06

ACTION – Antimicrobial peptide isolated from the Korean frog *Bufo bufo gargarizans*, with potent and broad-spectrum activity against Gram-positive and Gram-negative bacteria and fungi. It was more potent than the reference compound magainin 2 against *Staphylococcus aureus* and *Salmonella typhimurium*. Another exemplified peptide is:

Threonyl-arginyl-seryl-seryl-arginyl-alanyl-glycyl-leucyl-glutaminy-phenylalanyl-prolyl-valyl-glycyl-arginyl-valyl-histidyl-histidyl-leucyl-leucyl-leucyl-leucyl-lysine

264038: C112-H189-N37-O27

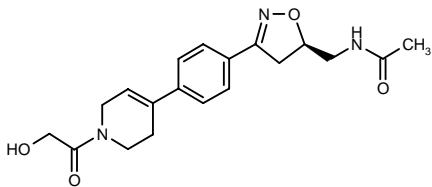
SOURCE – Samyang Genex.

REFERENCES

1. Kim, S.C. et al. (Samyang Genex Co., Ltd.) A novel antimicrobial peptide isolated from *Bufo bufo gargarizans*. WO 9807440.

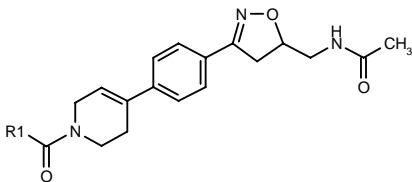
263298

N-[3-[4-[1-(2-Hydroxyacetyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl]-4,5-dihydroisoxazol-5(*R*)-ylmethyl]acetamide

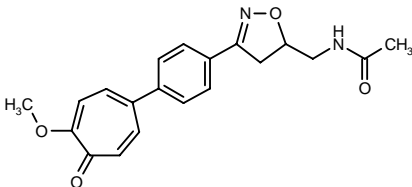


C19-H23-N3-O4; Mol wt: 357.41

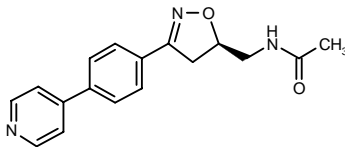
ACTION – Antibacterial agent active against Gram-positive bacteria including multiply resistant staphylococci and streptococci, as well as anaerobic organisms such as *Bacteroides* and *Clostridium* spp., and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. It exhibited MIC values of 2, 4 and 0.5 µg/ml, respectively, when tested against *Staphylococcus aureus* VC9213, *Enterococcus faecalis* UC9217 and *Streptococcus pneumoniae* UC9912. *In vivo*, it protected mice infected with *S. aureus* UC9213 from death after p.o. or s.c. administration. Within this series of specifically claimed isoxazoline derivatives, the following are also included:



Compound	R1	Isomer	Formula
264001	CH2OH		C ₁₉ H ₂₃ N ₃ O ₄
264002	OMe	R	C ₁₉ H ₂₃ N ₃ O ₄
264003	Me		C ₁₉ H ₂₃ N ₃ O ₃



264000: C20-H20-N2-O4



264004: C17-H17-N3-O2

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Barbachyn, M.R. et al. (Pharmacia & Upjohn Co.) Isoxazoline derivs. useful as antimicrobials. WO 9807708.

263821

Polypeptide with 341 amino acids of the tryptophanyl tRNA synthetase (trpS) family

ACTION – Novel tryptophanyl-tRNA synthetase (trpS; also known as tryptophan-tRNA ligase) polypeptide from *Streptococcus pneumoniae* with potential as a diagnostic reagent, for screening compounds with antibacterial activity and for use as a vaccine to induce immunization against bacteria, especially *S. pneumoniae*. Also disclosed is the use of inhibitors of this polypeptide (including antibodies) as antibacterial agents, for the treatment of otitis media, conjunctivitis, pneumonia, bacteremia, sinusitis, endocarditis, and particularly meningitis.

SOURCE – SmithKline Beecham.

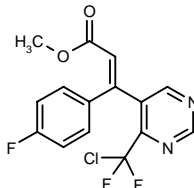
REFERENCES

1. Gentry, D.R. et al. (SmithKline Beecham Corp.) Novel trpS. WO 9810652.

ANTIFUNGAL AGENTS

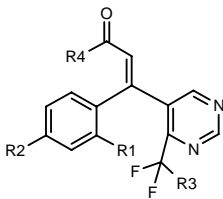
261843

3-[4-(Chlorodifluoromethyl)pyrimidin-5-yl]-3-(4-fluorophenyl)-2(*E*)-propenoic acid methyl ester



C15-H10-Cl-F3-N2-O2; Mol wt: 342.70

ACTION – Antifungal agent with an MIC value of 25 µg/ml against *Candida albicans* ATCC 10231. LD₅₀ > 400 mg/kg i.v. and > 1000 mg/kg p.o. in mice. Within this series of cinnamic acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	Isomer	Formula
263405	H	Cl	F	OMe	E	C ₁₅ H ₁₀ ClF ₃ N ₂ O ₂
263406	H	Cl	F	OMe	Z	C ₁₅ H ₁₀ ClF ₃ N ₂ O ₂
263407	Cl	Cl	Cl	OMe	E,Z	C ₁₅ H ₉ Cl ₃ F ₂ N ₂ O ₂
263408	H	F	Cl	OMe	Z	C ₁₅ H ₁₀ ClF ₃ N ₂ O ₂
263409	H	Me	Cl	OMe	E	C ₁₆ H ₁₃ ClF ₂ N ₂ O ₂
263410	H	OMe	Cl	OMe	E,Z	C ₁₆ H ₁₃ ClF ₂ N ₂ O ₃
263411	H	F	Cl	OH	E	C ₁₄ H ₈ ClF ₃ N ₂ O ₂
263412	H	F	Cl	i-PrO	E	C ₁₇ H ₁₄ ClF ₃ N ₂ O ₂
263413	H	F	Cl	cyclohexyl-O	E	C ₂₀ H ₁₈ ClF ₃ N ₂ O ₂
263414	H	F	Cl	OPh	E	C ₂₀ H ₁₂ ClF ₃ N ₂ O ₂
263415	H	F	Cl	OCH ₂ Ph	E	C ₂₁ H ₁₄ ClF ₃ N ₂ O ₂
263416	H	F	Cl	NH ₂	E	C ₁₄ H ₉ ClF ₃ N ₃ O
263417	H	F	Cl	4-morpholinyl	E	C ₁₈ H ₁₅ ClF ₃ N ₃ O ₂

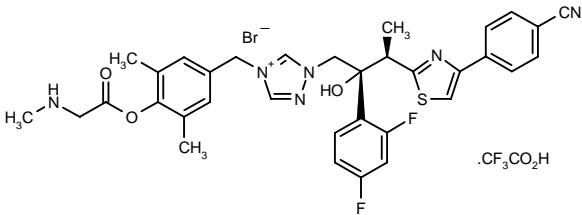
SOURCE – Nippon Soda.

REFERENCES

1. ADachi, H. et al. (Nippon Soda Co., Ltd.) *Novel cinnamonic acid derivs., their preparation method and antifungal agents.* JP 98029982.

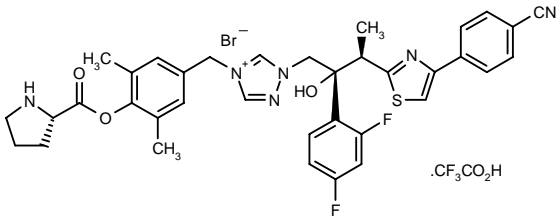
262115

1-[3(R)-[4-(4-Cyanophenyl)thiazol-2-yl]-2(R)-(2,4-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[2-(methylamino)acetoxy]benzyl]-1 H-1,2,4-triazolium bromide trifluoroacetate

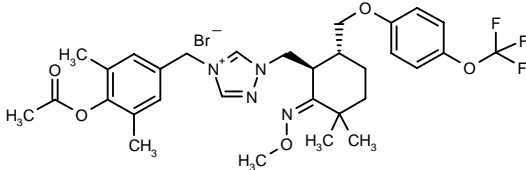


C34-H33-Br-F2-N6-O3-S.C2-H-F3-O2; Mol wt: 837.66

ACTION – Water-soluble antifungal agent with potent *in vivo* activity in rat models of systemic candidiasis (ED₅₀ = 4.6 μmol/kg i.v. and 4.7 μmol/kg p.o.), pulmonary aspergillosis (ED₅₀ = 8.0 μmol/kg i.v. and 17 μmol/kg p.o.) and systemic aspergillosis (ED₅₀ = 17 μmol/kg i.v. and 19 μmol/kg p.o.). Particularly suitable for parenteral administration. Other compounds from this series of *N*-benzylimidazolium and *N*-benzyltriazolium derivatives include the following:



263390: C36-H35-Br-F2-N6-O3-S.C2-H-F3-O2



263391: C31-H38-Br-F3-N4-O5

Compounds of the invention are converted *in vivo* to azoles such as ketoconazole and itraconazole.

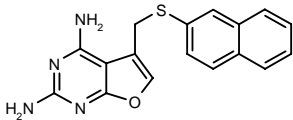
SOURCE – Roche.

REFERENCES

1. Ichihara, S. et al. (F. Hoffmann-La Roche AG) *N-Benzylimidazolium and N-benzyltriazolium derivs., their preparation and their use as antifungal and antimycotic agents.* EP 829478.

263128

5-(2-Naphthylsulfanylmethyl)furo[2,3-*d*]pyrimidine-2,4-diamine



C17-H14-N4-O-S; Mol wt: 322.38

Light pinkish solid, m.p. 233-5 °C (decomp.).

ACTION – Potent and selective inhibitor of *Pneumocystis carinii* dihydrofolate reductase (DHFR; IC₅₀ = 0.65 μM), exhibiting selectivity relative to rat liver DHFR (IC₅₀ = 12.3 μM) and *Toxoplasma gondii* DHFR (IC₅₀ = 11.6 μM). Title compound is currently undergoing preclinical evaluation in animal models of *P. carinii* pneumonia.

SOURCES – Duquesne Univ., Pittsburgh, PA (US); Hauptman-Woodward Med. Res. Inst., Buffalo, NY (US); Indiana Univ., Indianapolis, IN (US).

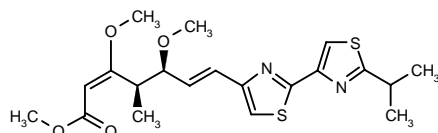
REFERENCES

1. Gangjee, A. et al. *Selective Pneumocystis carinii dihydrofolate reductase inhibitors: Design, synthesis, and biological evaluation of new 2,4-diamino-5-substituted-furo[2,3-d]pyrimidines.* J Med Chem 1998, 41(8): 1263.

CYSTOTHIAZOLE A

262031

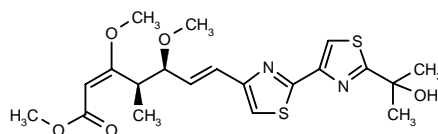
7-[2-(2-Isopropylthiazol-4-yl)thiazol-4-yl]-3,5(S)-dimethoxy-4-methyl-2(E),6(E)-heptadienoic acid methyl ester



C20-H26-N2-O4-S2; Mol wt: 422.56

Colorless needles, m.p. 111-2 °C, $[\alpha]_D^{25} +109^\circ$ (c 0.24, CHCl₃).

ACTION – Broad-spectrum antifungal antibiotic isolated from culture broths of the myxobacterium *Cystobacter fuscus* AJ-13278, structurally related to myxothiazol. Cystothiazole A demonstrated potent inhibition of *Phytophthora capsici* and also inhibited the growth of other fungi such as *Candida albicans*, *Saccharomyces cerevisiae* and *Aspergillus fumigatus*, whereas it was inactive against bacteria. It also showed *in vitro* cytotoxicity against human tumor cells, although it was much less potent than myxothiazol, with an IC₅₀ of 130 ng/ml against human colon carcinoma HCT-116 cells and of 110 ng/ml against human leukemia K562 cells. It appears to act by inhibiting submitochondrial NADH oxidation, giving an IC₅₀ of 1.8 μM for inhibition of NADH oxidase in submitochondrial membrane fractions. Another related compound from this source is:



Cystothiazole B [262032]: C20-H26-N2-O5-S2

SOURCE – Ajinomoto.

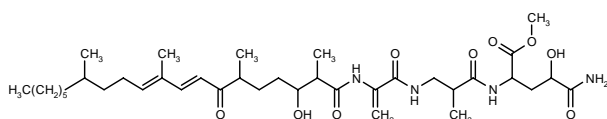
REFERENCES

1. Ojika, M. et al. *Cystothiazoles A and B, new bithiazole-type antibiotics from the myxobacterium Cystobacter fuscus*. J Antibiot 1998, 51(3): 275.

YM-170320

263211

5-Amino-4-hydroxy-2-[3-[2-(3-hydroxy-2,6,10,14-tetramethyl-7-oxo-8,10-icosadienamido)-2-propenamido]-2-methylpropionamido]-5-oxopentanoic acid methyl ester



C37-H62-N4-O9; Mol wt: 706.92

White powder, $[\alpha]_D^{25} -38.0^\circ$ (c 0.10, MeOH).

ACTION – Lipopeptide antibiotic produced by unidentified fungal strain YL-03706F, found to produce morphological changes in mutant *Candida tropicalis* pK233 colonies similar to those induced by the ergosterol biosynthesis inhibitor miconazole (0.1 μg/ml) at concentrations of up to 100 μg/ml, although it did not affect the growth of yeasts and filamentous fungi; it is thought that title compound also acts by inhibiting ergosterol biosynthesis.

SOURCE – Yamanouchi.

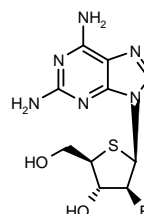
REFERENCES

1. Sugawara, T. et al. *YM-170320, a novel lipopeptide antibiotic inducing morphological change of colonies in a mutant of Candida tropicalis pK233*. J Antibiotic 1998, 51(4): 435.

ANTIVIRAL DRUGS

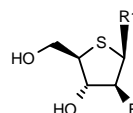
257218

2,6-Diamino-9-(2-deoxy-2-fluoro-4-thio-β-D-arabino-furanosyl)purine



C10-H13-F-N6-O2-S; Mol wt: 300.31

ACTION – Antiviral agent with potent *in vitro* activity in inhibiting the growth of herpesviruses such as herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV) and human cytomegalovirus (HCMV) in fibroblasts derived from human fetal lung, with respective ED₅₀ values of 0.0057, 0.050, 0.101 and 0.066 μg/ml (aciclovir: 0.14, 0.23, 2.72 and 6.9 μg/ml, respectively; ganciclovir: 0.016, 0.039, 3.1 and 0.21 μg/ml, respectively). Other representative compounds within this series of 9-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)purine derivatives include the following:



Compound	R1	Formula
262714	adenin-9-yl	C ₁₀ H ₁₂ FN ₅ O ₂ S
262715	guanin-9-yl	C ₁₀ H ₁₂ FN ₅ O ₃ S

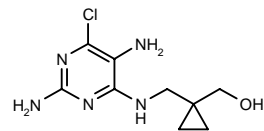
SOURCE – Yamasa.

REFERENCES

1. Yamada, K. et al. (Yamasa Corp.) *9-(2-Deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)-purine derivs*. WO 9737993.

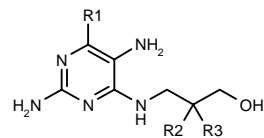
258443

1-[1-(2,5-Diamino-6-chloropyrimidin-4-ylaminomethyl)-cyclopropyl]methanol



C9-H14-Cl-N5-O; Mol wt: 243.70

ACTION – Antiviral agent for the treatment of rotavirus infections with potent activity against rotavirus SA-11 in CV-1 cells (IC₅₀ = 1.5 µg/ml) and low cytotoxicity in uninfected CV-1 cells (CC₅₀ > 100 µg/ml). LD > 1000 mg/kg p.o. in mice. Within this series of pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
263004	Cl	Et	Et	C ₁₁ H ₂₀ ClN ₅ O
263005	OH	-CH2CH2-		C ₉ H ₁₅ N ₅ O ₂
263006	Cl	H	H	C ₇ H ₁₂ ClN ₅ O

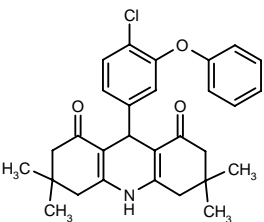
SOURCE – Nippon Shoji.

REFERENCES

1. Kuki, M. et al. (Nippon Shoji Co., Ltd.) *Novel pyrimidine cpds. and anti-rotavirus agents*. EP 806418, JP 97301958.

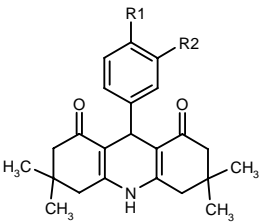
262080

9-(4-Chloro-3-phenoxyphenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione



C29-H30-Cl-N-O3; Mol wt: 476.01

ACTION – Antiviral agent for the treatment or prevention of herpes simplex virus (HSV) infections that acts by inhibiting HSV thymidine kinase (TK), with IC₅₀ values of 0.3 and 0.095 nmol, respectively, against HSV-1 TK and HSV-2 TK. Within this series of xanthene and acridine derivatives, the following are also included:



Compound	R1	R2	Formula
263418	Cl	SPh	C ₂₉ H ₃₀ ClNO ₂ S
263419	Cl	Ph	C ₂₉ H ₃₀ ClNO ₂
263420	Cl	Cl	C ₂₉ H ₂₅ Cl ₂ NO ₂
263421	Cl	F	C ₂₉ H ₂₅ ClFNO ₂
263422	Cl	1-pyrrolyl	C ₂₇ H ₂₉ ClN ₂ O ₂
263423	H	OPh	C ₂₉ H ₃₁ NO ₃
263424	Br	H	C ₂₉ H ₂₆ BrNO ₂
263425	Cl	4-Pyr-O	C ₂₈ H ₂₉ ClN ₂ O ₃
263426	NO2	OCH2Ph	C ₃₀ H ₃₂ N ₂ O ₅
263427	Cl	4-Pyr-S	C ₂₈ H ₂₉ ClN ₂ O ₂ S

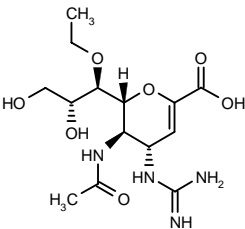
SOURCE – Roche.

REFERENCES

1. Martin, J.A. et al. (F. Hoffmann-La Roche AG) *Xanthene and acridine derivs. and their use*. EP 823426, JP 98067749.

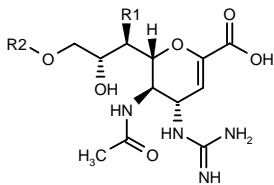
262081

5-Acetamido-2,3,4,5-tetradexoxy-7-O-ethyl-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid



C14-H24-N4-O7; Mol wt: 360.37

ACTION – Antiviral agent for the treatment of influenza and related viral infections with excellent sialidase (neuraminidase)-inhibitory activity (IC₅₀ = 7.0 nM against influenza A sialidase) and potent antiviral activity against the influenza A/Yamagata/32/89 strain in a plaque reduction assay (IC₅₀ = 0.8 nM). Other specifically claimed compounds from this series of neuraminic acid derivatives include the following:



Compound	R1	R2	Formula
263428	F	COC11H23	C ₂₄ H ₄₁ FN ₄ O ₇
263429	F	COC13H27	C ₂₆ H ₄₅ FN ₄ O ₇
263430	F	COC15H31	C ₂₈ H ₄₉ FN ₄ O ₇
263431	OMe	H	C ₁₃ H ₂₂ N ₄ O ₇
263432	OMe	COC13H27	C ₂₇ H ₄₈ N ₄ O ₈
263433	F	H	C ₁₂ H ₁₉ FN ₄ O ₆
263434	OEt	COC7H15	C ₂₂ H ₃₈ N ₄ O ₈
263435	OEt	COC11H23	C ₂₆ H ₄₆ N ₄ O ₈
263436	OEt	COC13H27	C ₂₈ H ₅₀ N ₄ O ₈
263437	OEt	COC15H31	C ₃₀ H ₅₄ N ₄ O ₈

SOURCE – Sankyo.

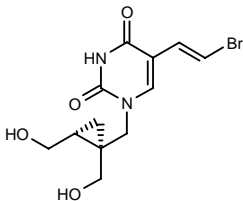
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1. Honda, T. et al. (Sankyo Co., Ltd.) *Neuraminic acid derivs., their preparation and their medical use.* EP 823428.

AV-100*

223499

1-[1(S),2(R)-Bis(hydroxymethyl)cyclopropylmethyl]-5-[2(E)-bromovinyl]uracil



C12-H15-Br-N2-O4; Mol wt: 331.17

ACTION – Orally bioavailable antiviral agent active against varicella-zoster virus (VZV). AV-100 exhibited superior antiherpetic activity against VZV than aciclovir (IC₅₀ = 0.031 and 3.4 µg/ml, respectively, against the Kawaguchi strain), and it also demonstrated 40-60-fold greater potency than aciclovir against a range of clinical isolates of VZV. It did not exhibit toxic effects in mice at doses up to 240 mg/kg/day i.v. for 6 days. Selected as a clinical candidate for the treatment of VZV infections.

SOURCE – Ajinomoto.

REFERENCES

1. Onishi, T. et al. (Ajinomoto Co., Inc.) *Bis(hydroxymethyl)cyclopropylmethyl pyrimidine derivs., their preparation and their use as anti-viral agents.* EP 649840, JP 95165731, US 5496824.

2. Tsuji, T. et al. *A novel potent anti-VZV pyrimidine nucleoside AV-100: Synthesis, antiherpetic activity and pharmacokinetics.* Antivir Res 1998, 37(3): Abst 10.

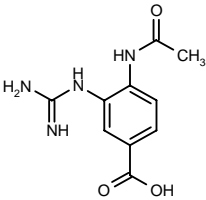
*Identified compound 223499 Drug Data Rep 1995, 17(9): 838.

BCX-140*

227474

4-Acetamido-3-guanidinobenzoic acid

BANA-113



C10-H12-N4-O3; Mol wt: 236.23

ACTION – Antiviral agent that selectively inhibits viral neuraminidase (sialidase) without affecting bacterial or mammalian neuraminidase. Compound inhibited enzyme from various influenza viruses with IC₅₀ values of 2-55 µM. *In vitro*, it inhibited the growth of influenza virus in MDCK cells, with IC₅₀ values in an MTT assay of 29-261 µM for most of the strains studied except for two H1N1 strains (no inhibition up to 500 µM); in the plaque inhibition assay, the IC₅₀ was about 30 µM for most strains except the above two strains (IC₅₀ > 100 µM).

SOURCES – Univ. Alabama, Birmingham, AL (US); BioCryst; Gilead.

REFERENCES

1. Babu, Y.S. et al. (BioCryst Pharm., Inc.) *Substd. benzene derivs. useful as neuraminidase inhibitors.* US 5602277, WO 9630329.

2. Luo, M. (Alabama Univ.) *Methods of inhibiting bacterial sialidase.* WO 9639838.

3. Luo, M. et al. (Alabama Univ.) *Inhibitors of influenza virus neuraminidase and methods of making and using the same.* US 5453533.

4. Bantia, S. et al. *Generation and characterization of a mutant of influenza A virus selected with the neuraminidase inhibitor BCX-140.* Antimicrob Agents Chemother 1998, 42(4): 801.

5. Brouillette, W.J. et al. *Structure-based benzoic acid inhibitors of influenza neuraminidase.* 214th ACS Natl Meet (Sept 7-11, Las Vegas) 1997, Abst MEDI 251.

6. Chand, P. et al. *Design and synthesis of benzoic acid derivatives as influenza neuraminidase inhibitors using structure-based drug design.* J Med Chem 1997, 40(25): 4030.

7. Singh, S. et al. *Structure-based inhibitors of influenza virus sialidase. A benzoic acid lead with novel interaction.* J Med Chem 1995, 38(17): 3217.

8. Sudbeck, E.A. et al. *Guanidinobenzoic acid inhibitors of influenza virus neuraminidase.* J Mol Biol 1997, 267(3): 584.

9. Williams, M. et al. *Synthesis and influenza neuraminidase inhibitory activity of aromatic analogues of sialic acid.* Bioorg Med Chem Lett 1995, 5(19): 2251.

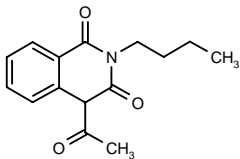
10. BioCryst Pharmaceuticals Annual Report 1994.

*Identified compound 227474 Drug Data Rep 1996, 18(3): 258.

LY-343814

262875

4-Acetyl-2-butyl-1,2,3,4-tetrahydroisoquinoline-1,3-dione



C15-H17-N-O3; Mol wt: 259.30

ACTION – Antiviral agent for the treatment of human rhinovirus (HRV) infections from a series of homophthalimides originally identified as inhibitors of HRV 3C protease. LY-343814 is an inhibitor of HRV14 2A protease (IC₅₀ = 19.7 μM), but showed little or no effect against HRV14 3C protease or HRV2 2A protease (IC₅₀ > 200 μM). It displayed antiviral activity in H1-HeLa cells inoculated with HRV14 (IC₅₀ = 4.2 μM) and low cytotoxicity (TC₅₀ = 125 μM; therapeutic index [TI] = 29.8).

SOURCE – Lilly.

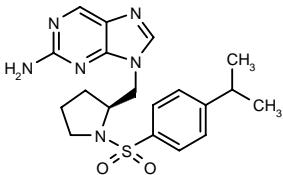
REFERENCES

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AIDS MEDICINES

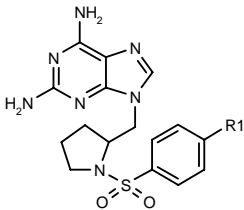
259196

9-[1-(4-Isopropylphenylsulfonyl)pyrrolidin-2(S)-ylmethyl]-purine-2-amine



C19-H24-N6-O2-S; Mol wt: 400.50

ACTION – Antiviral agent for AIDS with potent activity against HIV (HTLV-IIIB) in MT-4 cells (EC₅₀ = 4.2 μg/ml) and low cytotoxicity in uninfected cells (CC₅₀ > 200 μg/ml). Other compounds from this series of substituted purine derivatives include the following:



Compound	R1	Isomer	Formula
262997	i-Pr	S	C ₁₉ H ₂₈ N ₇ O ₂ S
262998	C(Me)2Et	S	C ₂₁ H ₂₉ N ₇ O ₂ S

Compound	R1	Isomer	Formula
262999	OMe	S	C ₁₇ H ₂₁ N ₇ O ₃ S
263000	CF3	S	C ₁₇ H ₁₈ F ₃ N ₇ O ₂ S
263001	OCF3	S	C ₁₇ H ₁₈ F ₃ N ₇ O ₃ S
263002	OCF3	racemic	C ₁₇ H ₁₈ F ₃ N ₇ O ₃ S

SOURCE – Nippon Paper.

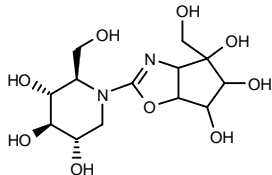
REFERENCES

1. Kojima, E. et al. (Nippon Paper Ind. Co., Ltd.) *9-Substd. purine derivs. and their use as antiviral agents*. JP 97316076.

260539

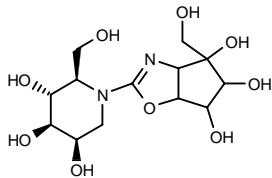
[2*R*-(2α,3β,4α,5β)]-1-[4,5,6-Trihydroxy-4-(hydroxymethyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopentoxazol-2-yl]-3,4,5-trihydroxy-2-(hydroxymethyl)piperidine

N-[4,5,6-Trihydroxy-4-(hydroxymethyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopentoxazol-2-yl]-1-deoxy-5-aza-D-glucopyranose



C13-H22-N2-O9; Mol wt: 350.32

ACTION – Agent for the treatment of HIV infection, obesity and diabetes that acts by virtue of its glycosidase-inhibitory activity. Another representative compound within this series of oxazoline derivatives is:



263202: C13-H22-N2-O9

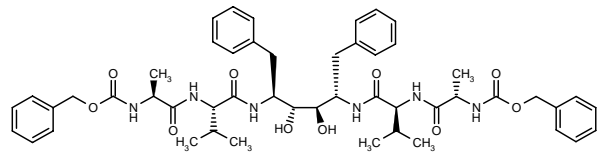
SOURCE – Sankyo.

REFERENCES

1. Shiozaki, M. (Sankyo Co., Ltd.) *Oxazoline cpds*. JP 98017565.

262028

*N*¹,*N*^{1'}-[3(*R*),4(*R*)-Dihydroxy-1,6-diphenylhexane-2(*S*),5(*S*)-diyl]bis(benzyloxycarbonyl-L-alanyl-L-valinamide)



C50-H64-N6-O10; Mol wt: 909.09

White solid.

ACTION – Antiviral agent for AIDS, an inhibitor of feline immunodeficiency virus (FIV) protease with K_i values for an autoproteolysis-resistant protease and mutant proteases of 8.3-41 nM and a K_i of 1.5 nM for wild-type HIV protease. In tissue culture, the compound at 1 µg/ml (1.1 µM) was able to almost completely block virus production in cells acutely infected with HIV, FIV and simian immunodeficiency virus (SIV). It was not toxic to cells, and after 2 months of culture there was no sign of resistance development by virus.

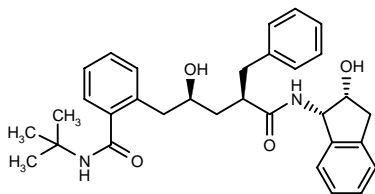
SOURCE – Scripps Res. Inst., La Jolla, CA (US).

REFERENCES

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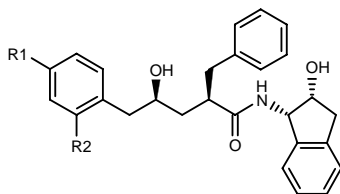
263164

2(R)-Benzyl-5-[2-(N-tert-butylcarbamoyl)phenyl]-4(S)-hydroxy-N-[2(R)-hydroxyindan-1(S)-yl]pentanamide



C32-H38-N2-O4; Mol wt: 514.66

ACTION – Antiviral agent for AIDS that acts by inhibiting HIV protease (IC_{50} in the range 1-6 nM), proven to inhibit HIV-1 replication in infected MT-4 cells (CIC_{95} = 800 nM). Other specifically claimed compounds include the following:



Compound	R1	R2	Formula
263403	H	t-BuNHCO	$C_{31}H_{38}N_2O_5$
263404	Me	t-BuNHCO	$C_{33}H_{40}N_2O_4$

SOURCE – Merck & Co.

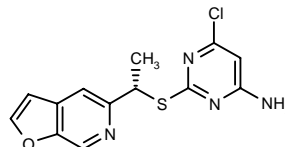
REFERENCES

1. Coburn, C.A. et al. (Merck & Co., Inc.) HIV protease inhibitors useful for the treatment of AIDS. US 5747540.

PNU-142721*

245740

(-)-(S)-6-Chloro-2-[1-(furo[2,3-c]pyridin-5-yl)ethyl-sulfanyl]pyrimidine-4-amine



C13-H11-Cl-N4-O-S; Mol wt: 306.77

ACTION – Potent and specific, non-nucleoside HIV-1 reverse transcriptase inhibitor (IC_{50} = 0.02 µM against wild-type enzyme) with potent inhibitory activity against a range of mutant enzymes (IC_{50} = 0.017-0.179 µM). It demonstrated antiviral activity against wild-type HIV-1_{IIIB} in MT-4 cells (IC_{90} = 0.001 µM) and against a range of mutant HIV-1 variants resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (IC_{90} = 0.008-1.1 µM). Favorable pharmacokinetics were observed in rats following either systemic or oral administration, with an absolute oral bioavailability of over 90% following doses of 30-80 mg/kg and high brain levels (75% of those in plasma) following a dose of 15 mg/kg i.v. PNU-142721 has been selected as a candidate for clinical development.

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Nugent, R.A. et al. (Pharmacia & Upjohn Co.) α -Subst. pyrimidine-thioalkyl and alkylether cpds. as inhibitors of viral reverse transcriptase. EP 824524, WO 9635678.

2. Olmsted, R.A. et al. Antiviral activity profiling of the furopyridine-thiopyrimidine, PNU-142721: A novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor. Antivir Res 1998, 37(3): Abst 46.

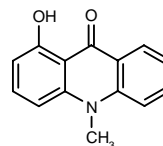
3. Wishka, D.G. et al. (-)-6-Chloro-2-[(1-furo[2,3-c]pyridin-5-ylethyl)thio]-4-pyrimidinamine, PNU-142721, a new broad spectrum HIV-1 non-nucleoside reverse transcriptase inhibitor. J Med Chem 1998, 41(9): 1357.

*Identified compound 245740 (see 245355) Drug Data Rep 1997, 19(3): 256.

RD6-5071

263680

1-Hydroxy-10-methyl-9(10H)-acridinone



C14-H11-N-O2; Mol wt: 225.25

ACTION – Antiviral agent for AIDS shown to suppress the TNF- α -induced expression of HIV-1 in OM-10.1 cells with an EC_{50} of 2.0 µg/ml and to inhibit the expression of HIV-1 in chronically infected U1 cells. It also inhibited the replication of HIV-1 in acutely infected U937 and peripheral blood mononuclear cells. Compound inhibited protein kinase C (PKC) and was suggested to inhibit the activity of the HIV-1 genome by blocking a signal transduction pathway involving PKC activation.

SOURCES – Rational Drug Design Labs.; Yamasa.

REFERENCES

1. Fujiwara, M. et al. *Acridone derivatives are transcriptional inhibitors of human immunodeficiency virus type 1 (HIV-1)*. *Antivir Res* 1998, 37(3): Abst 53.

W61D gp120

263632

Vaccine consisting of recombinant gp120 (W61D) in SBN₁ adjuvant consisting of an emulsion (SB26) mixed with monophosphoryl lipid A and QS21

ACTION – Recombinant HIV-1 gp120 envelope vaccine proven to induce a strong immune response, inducing high titers of binding and neutralizing antibodies against the homologous HIV-1 (HIV-1_{W61D}) and 10-fold lower titers against heterologous challenge virus (SHI_{VSF33}), a simian immunodeficiency virus modified with *env*, *tat* and *rev* genes from HIV-1_{SF33}. Despite the strong immune response, the vaccine was unable to protect macaques against infection by SHI_{VSF33}. The vaccine is currently undergoing clinical trials in the U.K.

SOURCE – SmithKline Beecham.

REFERENCES

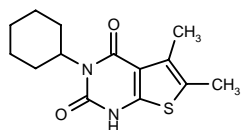
1. Stott, E.J. et al. *Evaluation of a candidate human immunodeficiency virus type 1 (HIV-1) vaccine in macaques: Effect of vaccination with HIV-1 gp120 on subsequent challenge with heterologous simian immunodeficiency virus-HIV-1 chimeric virus*. *J Gen Virol* 1998, 79(Part 3): 423.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

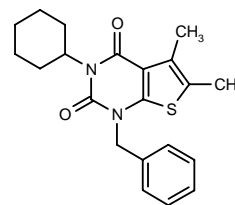
262045

3-Cyclohexyl-5,6-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione



C14-H18-N2-O2-S; Mol wt: 278.37

ACTION – Analgesic and antiinflammatory agent, as demonstrated by inhibition of phenylquinone-induced writhing in mice (46% protection at 10 mg/kg p.o.), carrageenan-induced rat paw edema (59% protection at 100 mg/kg p.o.) and acetic acid-induced peritonitis in rats (51% protection at 10 mg/kg p.o.). Compound was more potent than mefenamic acid but did not show any ulcerogenic activity or hyperemia. Another thienopyrimidine is:



262046: C21-H24-N2-O2-S

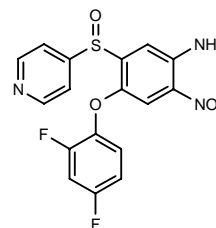
SOURCE – Univ. Catania, Catania (IT).

REFERENCES

1. Romeo, G. et al. *Synthesis of new thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones with analgesic and anti-inflammatory activities*. *Arzneim-Forsch-Drug Res* 1998, 48(2): 167.

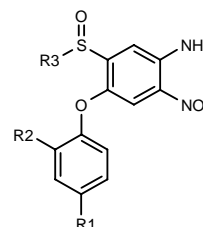
262824

4-(2,4-Difluorophenoxy)-2-nitro-5-(4-pyridylsulfinyl)aniline



C17-H11-F2-N3-O4-S; Mol wt: 391.35

ACTION – Agent for the treatment of autoimmune, inflammatory, allergic and bone disorders, an inhibitor of the production of inflammatory cytokines. *In vitro*, it inhibited the concanavalin A (ConA)-stimulated production of IL-1 β and IL-6 in human peripheral blood (100% inhibition at 1 μ g/ml in both cases), as well as the ConA-stimulated production of IL-5 in murine spleen cells (93% inhibition at 0.3 μ g/ml). Within this series of nitroaniline compounds, the following are also included:



Compound	R1	R2	R3	Formula
263082	H	H	3-F-Ph	C ₁₈ H ₁₃ FN ₂ O ₄ S
263083	F	F	3-F-Ph	C ₁₈ H ₁₁ F ₃ N ₂ O ₄ S
263084	H	Ph	4-Pyr	C ₂₃ H ₁₇ N ₃ O ₄ S

SOURCE – Taisho.

REFERENCES

1. Saito, H. et al. (Taisho Pharm. Co., Ltd.) *4-Aryloxy-5-arylthionitroaniline cpds*. JP 98077260.

SOURCES – Rational Drug Design Labs.; Yamasa.

REFERENCES

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SOURCE – SmithKline Beecham.

REFERENCES

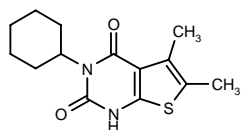
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

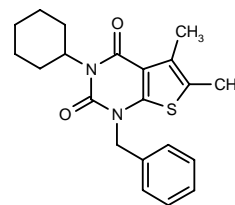
262045

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C14-H18-N2-O2-S; Mol wt: 278.37

ACTION – Analgesic and antiinflammatory agent, as demonstrated by inhibition of phenylquinone-induced writhing in mice (46% protection at 10 mg/kg p.o.), carrageenan-induced rat paw edema (59% protection at 100 mg/kg p.o.) and acetic acid-induced peritonitis in rats (51% protection at 10 mg/kg p.o.). Compound was more potent than mefenamic acid but did not show any ulcerogenic activity or hyperemia. Another thienopyrimidine is:



262046: C21-H24-N2-O2-S

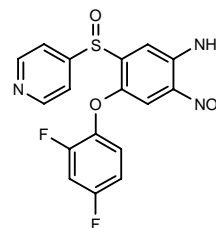
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REFERENCES

1. Romeo, G. et al. *Synthesis of new thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones with analgesic and anti-inflammatory activities*. *Arzneim-Forsch-Drug Res* 1998, 48(2): 167.

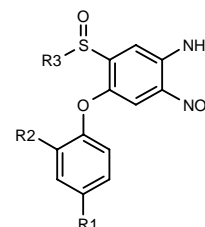
262824

4-(2,4-Difluorophenoxy)-2-nitro-5-(4-pyridylsulfinyl)aniline



C17-H11-F2-N3-O4-S; Mol wt: 391.35

ACTION – Agent for the treatment of autoimmune, inflammatory, allergic and bone disorders, an inhibitor of the production of inflammatory cytokines. *In vitro*, it inhibited the concanavalin A (ConA)-stimulated production of IL-1 β and IL-6 in human peripheral blood (100% inhibition at 1 μ g/ml in both cases), as well as the ConA-stimulated production of IL-5 in murine spleen cells (93% inhibition at 0.3 μ g/ml). Within this series of nitroaniline compounds, the following are also included:



Compound	R1	R2	R3	Formula
263082	H	H	3-F-Ph	C ₁₈ H ₁₃ FN ₂ O ₄ S
263083	F	F	3-F-Ph	C ₁₈ H ₁₁ F ₃ N ₂ O ₄ S
263084	H	Ph	4-Pyr	C ₂₃ H ₁₇ N ₃ O ₄ S

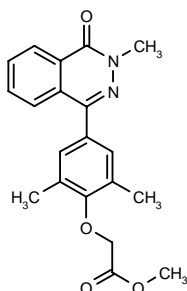
SOURCE – Taisho.

REFERENCES

1. Saito, H. et al. (Taisho Pharm. Co., Ltd.) *4-Aryloxy-5-arylthionitroaniline cpds*. JP 98077260.

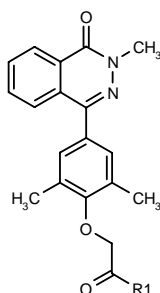
262917

2-[2,6-Dimethyl-4-(3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)phenoxy]acetic acid methyl ester



C20-H20-N2-O4; Mol wt: 352.39

ACTION – An inhibitor of matrix metalloproteinases such as stromelysin, collagenase and gelatinase and of the release of tumor necrosis factor (TNF- α), also reported to inhibit the shedding of TNF receptor, IL-6 receptor and L-selectin. Potentially useful in the treatment of rheumatoid arthritis, osteoarthritis and other inflammatory and autoimmune disorders, as well as cancer. Other specifically claimed compounds from this series of hydroxamic and carboxylic acid derivatives include the following:



Compound	R1	Formula
263186	OH	C ₁₉ H ₁₈ N ₂ O ₄
263187	NHOH	C ₁₉ H ₁₉ N ₃ O ₄

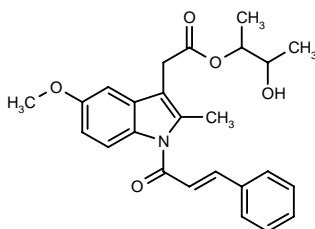
SOURCE – Chiroscience.

REFERENCES

1. Owen, D.A. et al. (Chiroscience, Ltd.) *Hydroxamic and carboxylic acid derivs. having MMP and TNF inhibitory activity.* WO 9805635.

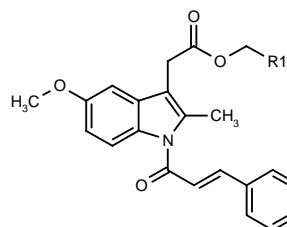
263162

2-(1-Cinnamoyl-5-methoxy-2-methylindol-3-yl)acetic acid 2-hydroxy-1-methylpropyl ester



C25-H27-N-O5; Mol wt: 421.49

ACTION – An ester of the antiinflammatory and analgesic agent cinmetacin with significantly reduced potential for inducing gastric ulcers than the parent compound, but with the advantage of retaining the activity of cinmetacin. In particular, test compound caused 52% inhibition of carrageenan-induced rat paw edema at 100 mg/kg p.o. vs. 65% inhibition with cinmetacin at the same dose. Analgesic activity was comparable: ED₅₀ = 31.0 mg/kg p.o. vs. 36.0 mg/kg p.o. for cinmetacin in the acetic acid-induced writhing test in mice. In contrast, it showed significantly reduced ulcerogenic activity in rats (UD₅₀ = 175.0 mg/kg p.o. vs. 18.0 mg/kg p.o. for cinmetacin and 14.0 mg/kg p.o. for sulindac). Other specifically claimed esters of cinmetacin include the following:



Compound	R1	Formula
263465	CH=CHCH2OH	C ₂₅ H ₂₅ NO ₅
263466	2-THP	C ₂₇ H ₂₉ NO ₅

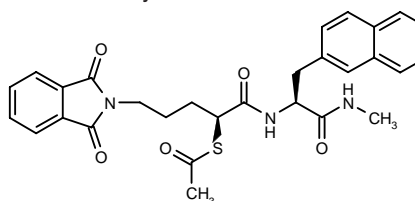
SOURCE – Samjin.

REFERENCES

1. Cho, E.H. et al. (Samjin Pharm. Co., Ltd.) *N-Cinnamoyl-2-methyl-5-methoxy-3-indoleacetic acid ester, and pharmaceutical preparation containing the same.* US 5747521, WO 9406769.

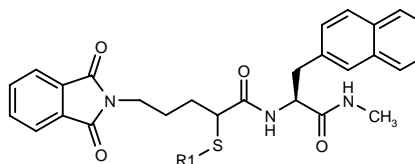
263249

N-[2(S)-(Acetylsulfanyl)-5-phthalimidopentanoyl]-L-2-naphthylalanine methylamide



C29-H29-N3-O5-S; Mol wt: 531.63

ACTION – Agent for the treatment of degenerative diseases and certain cancers that inhibits matrix metalloproteinases such as collagenase and gelatinase and tumor necrosis factor (TNF) production. Other specifically claimed peptidyl compounds include the following:



Compound	R1	Isomer	Formula
263552	Ac	R	C ₂₉ H ₂₉ N ₃ O ₅ S
263553	Ac		C ₂₉ H ₂₉ N ₃ O ₅ S
263554	H	R	C ₂₇ H ₂₇ N ₃ O ₄ S
263555	H	S	C ₂₇ H ₂₇ N ₃ O ₄ S
263556	H		C ₂₇ H ₂₇ N ₃ O ₄ S

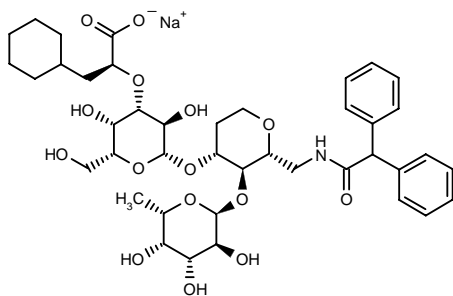
SOURCE – Chiroscience.

REFERENCES

1. Baxter, A.D. and Montana, J.G. (Chiroscience, Ltd.) *Peptidyl cpds. having MMP and TNF inhibitory activity*. WO 9806696.

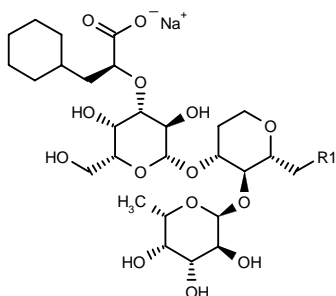
263264

3-Cyclohexyl-2-(S)-[O-(6-deoxy- α -L-galactopyranosyl)-(1 \rightarrow 4)-O-[1,2,6-trideoxy-6-(2,2-diphenylacetamido)-D-glucopyranosyl]-(3 \rightarrow 1)- β -D-galactopyranos-3-O-yl]propionic acid sodium salt

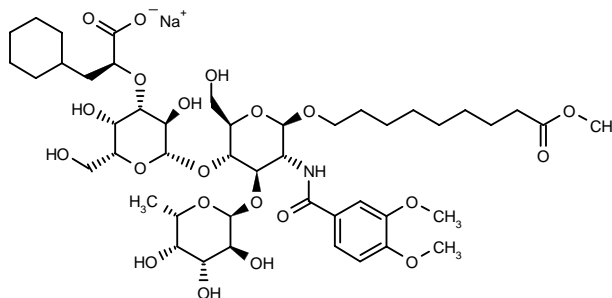


C41-H56-N-Na-O15; Mol wt: 825.88

ACTION – Agent for the treatment of acute or chronic inflammatory and autoimmune diseases such as rheumatoid arthritis, asthma, allergy, psoriasis, dermatitis, acute respiratory distress syndrome (ARDS), inflammatory bowel disease and ophthalmic inflammatory diseases, as well as septic shock, thrombosis, myocardial infarction, reperfusion injury, stroke, multiple sclerosis, metastatic cancer and transplant rejection, a sialyl Lewis X (SLe^x) and sialyl Lewis A (SLe^a) mimetic proven to inhibit the binding of E-selectin to SLe^a. Other compounds from this series of oligosaccharides include the following:



Compound	R1	Formula
263904	OH	C ₂₇ H ₄₆ NaO ₁₅
263905	NHCONHPh	C ₃₄ H ₅₁ N ₂ NaO ₁₅



263903: C46-H72-N-Na-O21

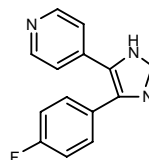
SOURCE – Novartis.

REFERENCES

1. Thoma, G. et al. (Novartis AG) *Modified oligosaccharides*. WO 9806730.

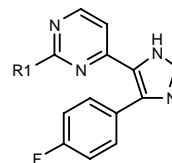
263276

4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazole



C14-H10-F-N3; Mol wt: 239.25

ACTION – An inhibitor of the production of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF), as well as proinflammatory proteins such as cyclooxygenase type 2 (COX-2), that acts by virtue of its CSBP/p38/RK kinase-inhibitory activity. Claimed for use in the treatment of arthritis, osteoporosis, asthma, diabetic retinopathy, tumor growth and metastasis, and atherosclerosis. Within this series of specifically claimed imidazole derivatives, the following are also included:



Compound	R1	Formula
264010	OMe	C ₁₄ H ₁₁ FN ₃ O
264011	Sme	C ₁₄ H ₁₁ FN ₃ S

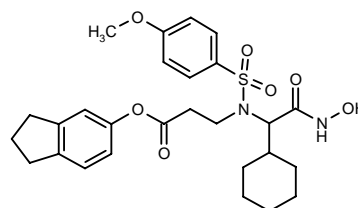
SOURCE – SmithKline Beecham.

REFERENCES

1. Adams, J.L. and Boehm, J.C. (SmithKline Beecham Corp.) *Imidazole cpds., compsns. and use*. WO 9807425.

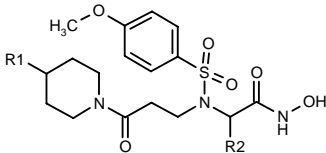
263292

3-[N-[1-Cyclohexyl-1-(N-hydroxycarbonyl)methyl]-N-(4-methoxyphenylsulfonyl)amino]propionic acid 5-indanyl ester



C27-H34-N2-O7-S; Mol wt: 530.63

ACTION – An inhibitor of matrix metalloproteinases and tumor necrosis factor (TNF) production, claimed for use in the treatment of arthritis, cancer, tissue ulceration, restenosis, AIDS, septic shock and other diseases characterized by matrix metalloproteinase activity or involving the production of TNF. A compound within a series of specifically claimed arylsulfonylamino hydroxamic acid derivatives, wherein the following are also included:



Compound	R1	R2	Formula
265046	OAc	i-Pr	C ₂₂ H ₃₃ N ₃ O ₆ S
265047	OH	cyclohexyl	C ₂₃ H ₃₅ N ₃ O ₇ S
265048	OCOPh	i-Pr	C ₂₇ H ₃₅ N ₃ O ₆ S
265049	OH	i-Pr	C ₂₆ H ₃₁ N ₃ O ₇ S
265050	CO ₂ H	cyclohexyl	C ₂₄ H ₃₅ N ₃ O ₈ S
265051	CO ₂ Et	cyclohexyl	C ₂₆ H ₃₉ N ₃ O ₆ S

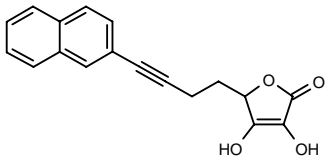
SOURCE – Pfizer.

REFERENCES

1. Blumenkopf, T.A. and Robinson, R.P. (Pfizer, Inc.) *Arylsulfonylamino hydroxamic acid derivs.* WO 9807697.

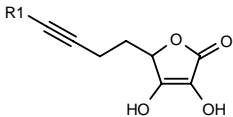
263301

3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butyryl]furan-2(5*H*)-one

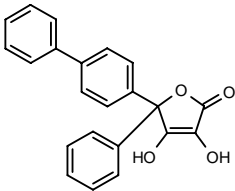


C18-H14-O4; Mol wt: 294.31

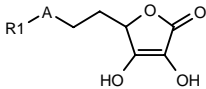
ACTION – Combined inhibitor of lipid peroxidation and arachidonic acid metabolism with potential in the treatment of chronic inflammatory disorders such as rheumatoid arthritis, asthma, inflammatory bowel disease, atherosclerosis, acute respiratory distress syndrome, and CNS disorders such as Alzheimer’s disease and Parkinson’s disease wherein reactive oxygen species and inflammatory mediators are contributing factors. *In vitro*, compound was found to inhibit 5-lipoxygenase (5-LO; 66% inhibition at 1 μM) and, to a much lesser extent, cyclooxygenase type 1 (COX-1; 34% inhibition at 300 μM) and COX-2 (23% inhibition at 300 μM). It inhibited lipid peroxidation by 75% at 300 μM using rat liver microsomes. In addition, compound was found to potently inhibit nuclear factor-κB (NF-κB) nuclear translocation in NR8383 cells stimulated with lipopolysaccharide (90% inhibition at 30 nM) and is reported to inhibit the action of inflammatory cytokines such as tumor necrosis factor-α (TNF-α). Within this series of specifically claimed 3,4-dihydroxy-2(5*H*)-furanones, the following are also included:



Compound	R1	Formula
263994	2-(PrCH=CHCH ₂)-Ph	C ₂₀ H ₂₂ O ₄
263995	2-(PhSCH ₂)-Ph	C ₂₁ H ₁₈ O ₄ S
263996	4-(4-F-Ph)-2-thienyl	C ₁₈ H ₁₃ FO ₄ S



263993: C22-H16-O4



Compound	R1	A	Formula
263997	4,5-(Ph)2-2-oxazolyl	S	C ₂₁ H ₁₇ NO ₅ S
263998	1-Naph	S	C ₁₆ H ₁₄ O ₄ S
263999	2-Naph	S	C ₁₆ H ₁₄ O ₄ S
264016	4-PhO-Ph	O	C ₁₈ H ₁₆ O ₆

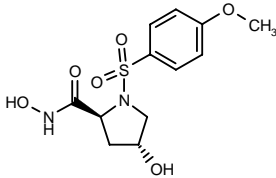
SOURCE – Oxis.

REFERENCES

1. Hopper, A.T. et al. (Oxis Intl., Inc.) *5-Substd. and 5,5-disubstd.-3,4-dihydroxy-2(5H)-furanones and methods of use therefor.* WO 9807714.

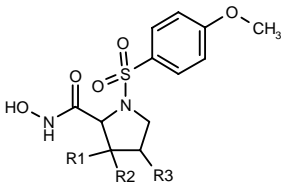
263339

N,4(*R*)-Dihydroxy-1-(4-methoxyphenylsulfonyl)-L-prolinamide



C12-H16-N2-O6-S; Mol wt: 316.33

ACTION – Agent for the treatment of osteoarthritis, periodontitis, corneal ulceration, tumor invasion and rheumatoid arthritis, an inhibitor of matrix metalloproteinases. Within this series of specifically claimed substituted cyclic amines, the following are also included:



Compound	R1=R2	R3	Isomer	Formula
264123	H	OH	2R,4R	C ₁₂ H ₁₆ N ₂ O ₆ S
264124	H	OH	2R,4S	C ₁₂ H ₁₆ N ₂ O ₆ S
264125	H	OH	2S,4S	C ₁₂ H ₁₆ N ₂ O ₆ S
264126	H	OMe	2R,4S	C ₁₃ H ₁₈ N ₂ O ₆ S
264127	H	1-Me-2-imidazolyl-S	2R,4R	C ₁₆ H ₂₀ N ₄ O ₅ S ₂
264128	H	3-Pyr-O	2R,4S	C ₁₇ H ₁₉ N ₃ O ₆ S
264129	Me	OH	2R,4R	C ₁₄ H ₂₀ N ₂ O ₆ S

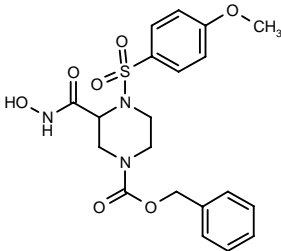
SOURCE – Procter & Gamble.

REFERENCES

1. Natchus, M.G. et al. (Procter & Gamble Co.) *Substd. cyclic amine metalloprotease inhibitors*. WO 9808815.

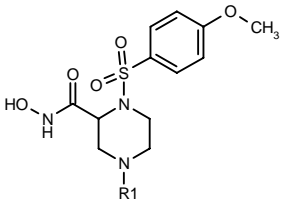
263347

4-(Benzyloxycarbonyl)-1-(4-methoxyphenylsulfonyl)-piperazine-2-carboxhydroxamic acid



C20-H23-N3-O7-S; Mol wt: 449.48

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, tumor metastasis and various ulcerative conditions that exerts its activity through the inhibition of matrix metalloproteinases. Within this series of 1,4-heterocyclic compounds, the following are also included:



Compound	R1	Formula
264291	Me	C ₁₃ H ₁₉ N ₃ O ₅ S
264292	4-morpholinyl-CO	C ₁₇ H ₂₄ N ₄ O ₇ S
264293	1-adamantyl-NHCO	C ₂₃ H ₃₂ N ₄ O ₆ S
264294	COCH2OPh	C ₂₀ H ₂₃ N ₃ O ₇ S

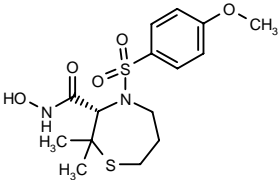
SOURCE – Procter & Gamble.

REFERENCES

1. De, B. et al. (Procter & Gamble Co.) *1,4-Heterocyclic metalloprotease inhibitors*. WO 9808825.

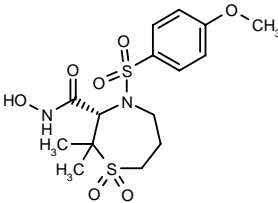
263349

4-(4-Methoxyphenylsulfonyl)-2,2-dimethylperhydro-1,4-thiazepine-3(R)-carboxhydroxamic acid



C15-H22-N2-O5-S2; Mol wt: 374.47

ACTION – Inhibitor of metalloproteases, particularly matrix metalloproteinases, with potential in the treatment or prevention of rheumatoid arthritis, osteoarthritis, tumor metastasis, ulcerative conditions, periodontal disease, fever, inflammation and multiple sclerosis. Another compound from this series of hydroxamic acid derivatives is:



264559: C15-H22-N2-O7-S2

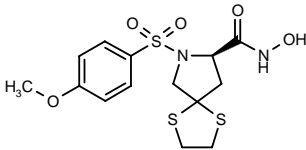
SOURCE – Procter & Gamble.

REFERENCES

1. De, B. et al. (Procter & Gamble Co.) *Heterocyclic metalloprotease inhibitors*. WO 9808827.

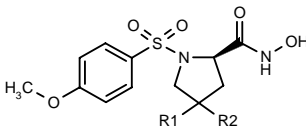
263366

7-(4-Methoxyphenylsulfonyl)-1,4-dithia-7-azaspiro[4.4]-nonane-8(R)-carboxhydroxamic acid

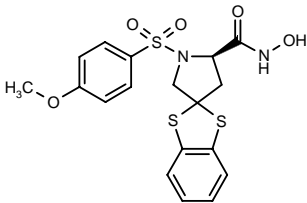


C14-H18-N2-O5-S3; Mol wt: 390.49

ACTION – Agent for the treatment of inflammatory disorders such as rheumatoid arthritis, osteoarthritis, tumor metastasis and various ulcerative conditions, an inhibitor of matrix metalloproteinases. Within this series of spirocyclic compounds, the following are also included:



Compound	R1,R2	Formula
264716	-SCH2CH2S-	C ₁₅ H ₂₀ N ₂ O ₅ S ₃
264717	-OCH2CH2O-	C ₁₄ H ₁₈ N ₂ O ₇ S
264718	-OCH2C(Me)2CH2O-	C ₁₇ H ₂₄ N ₂ O ₇ S
264719	-OCH2C(Et)2CH2O-	C ₁₉ H ₂₈ N ₂ O ₇ S
264720	-OCH2C(=CH2)CH2O-	C ₁₆ H ₂₀ N ₂ O ₇ S



264715: C18-H18-N2-O5-S3

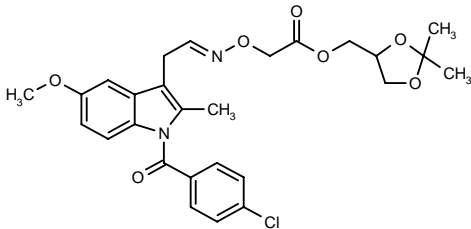
SOURCE – Procter & Gamble.

REFERENCES

1. Wang, Z. et al. (Procter & Gamble Co.) *Spirocyclic metalloprotease inhibitors*. WO 9808850.

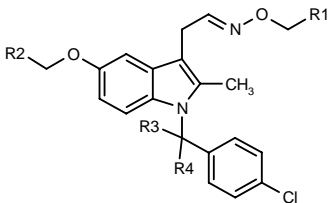
263490

2-[2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]ethylideneaminoxy]acetic acid 2,2-dimethyl-1,3-dioxolan-4-ylmethyl ester

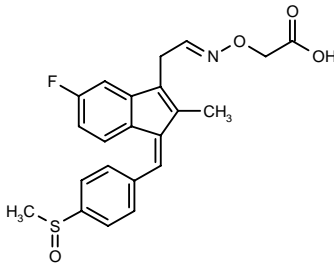


C27-H29-Cl-N2-O7; Mol wt: 528.99

ACTION – Antiinflammatory agent, an inhibitor of prostaglandin biosynthesis that acts preferentially by inhibiting cyclooxygenase type 2 (COX-2, also known as prostaglandin endoperoxide H synthase or PGHS-2), as demonstrated using recombinant human PGHS-1 and PGHS-2 (IC₅₀ = 0.09 and 0.003 μM, respectively). Other particularly preferred compounds within this series of specifically claimed oxime derivatives of indole and indene compounds include the following:



Compound	R1	R2	R3	R4	Formula
263590	CO2H	H	-O-		C ₂₁ H ₁₉ ClN ₂ O ₅
263591	CO2CH2-CH(OH)CH2OH	H	-O-		C ₂₄ H ₂₅ ClN ₂ O ₇
263592	CH2OH	H	-O-		C ₂₁ H ₂₁ ClN ₂ O ₄
263593	5-tetrazolyl	H	-O-		C ₂₁ H ₁₉ ClN ₆ O ₃
263594	CONH-CH2CH2OH	H	-O-		C ₂₃ H ₂₄ ClN ₃ O ₅
263595	CO2H	2-benzothiazolyl	H	H	C ₂₈ H ₂₄ ClN ₃ O ₄ S



263596: C22-H20-FNO-4S

SOURCE – Abbott.

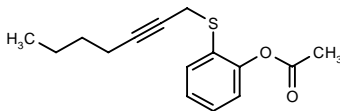
REFERENCES

1. Brooks, C.D.W. et al. (Abbott Labs.) *Oxime derivs. of indole and indene cpds. as inhibitors of prostaglandin biosynthesis*. US 5750558.

APHS

264275

Acetic acid 2-(2-heptynylsulfanyl)phenyl ester



C15-H18-O2-S; Mol wt: 262.37

ACTION – Potent, reversible and selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.8 μM against human COX-2; IC₅₀ = 17.0 μM against sheep COX-1; COX-1/COX-2 = 21) proven to inhibit lipopolysaccharide (LPS)- and interferon gamma-induced PGD₂ synthesis as a measure of COX-2 activity in cultured macrophages (IC₅₀ = 0.12 μM vs. 100 μM for aspirin). In contrast to other selective COX-2 inhibitors, APHS was more potent against a triple mutant than wild-type COX-2. The compound was also effective in inhibiting the growth of COX-2 inhibitor-sensitive human colon cancer HCA-7 cells (IC₅₀ = 2 μM), whereas it did not affect the growth of COX-2 inhibitor-insensitive human colon cancer HCT-15 cells. COX-2 selectivity was also demonstrated by inhibition of carrageenan-induced pouch PGE₂ synthesis without altering serum TxB₂ levels in rats.

SOURCES – Searle; Vanderbilt Univ., Nashville, TN (US).

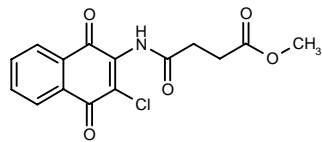
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1. Kalgutkar, A.S. et al. *Aspirin-like molecules that covalently inactive cyclooxygenase*.
2. Science 1998, 280(5367): 1268.

PP1D-1

262043

N-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-succinamic acid methyl ester



C15-H12-Cl-N-O5; Mol wt: 321.72

M.p. 174-5 °C.

ACTION – Antiinflammatory and antiallergic agent and platelet aggregation inhibitor shown to inhibit the aggregation of rabbit platelets induced by thrombin, PAF, collagen, arachidonic acid and U-46619 with IC₅₀ values of 17.9, 9.8, 3.9, 1.8 and 1.7 μM, respectively, and also to inhibit ATP release from stimulated platelets; compound did not affect cyclooxygenase and thromboxane synthase activities, but appeared to exert its antiplatelet effects mainly by inhibiting phosphoinositide turnover. It also displays *in vitro* antiinflammatory (inhibition of β-glucuronidase and lysozyme release from neutrophils at 0.1-1 μg/ml and of superoxide formation at 0.3-1 μg/ml) and antiallergic activity (inhibition of β-glucuronidase and histamine release from mast cells at 0.1-1 μg/ml). *In vivo*, it inhibited polymyxin B-induced paw edema in mice and ear edema caused by several agents after i.p. or p.o. administration, which was suggested to involve protection of the microvasculature against inflammatory mediators.

SOURCES – China Med. Coll., Taichung (TW); Natl. Taiwan Univ., Taipei (TW).

REFERENCES

1. Kuo, S.-C. et al. *Synthesis and cytotoxicity of 1,2-disubstituted naphth[2,3-d]-imidazole-4,9-diones and related compounds*. J Med Chem 1996, 39(7): 1447.

2. Liao, C.-H. et al. *Effect of PP1D-1, a synthetic antiplatelet compound, on rabbit platelets*. Jpn J Pharmacol 1998, 76(2): 141.

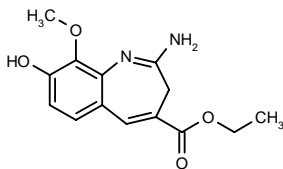
3. Lien, J.-C. et al. *Synthesis and antiplatelet, antiinflammatory, and antiallergic activities of 2-substituted 3-chloro-1,4-naphthoquinone derivatives*. Bioorg Med Chem 1997, 5(12): 2111.

4. Wang, J.P. et al. *Inhibition of hind-paw edema and cutaneous vascular plasma extravasation by 2-chloro-3-methoxycarbonylpropionamido-1,4-naphthoquinone (PP1D1) in mice*. Naunyn-Schmied Arch Pharmacol 1996, 354(6): 779.

IMMUNOLOGIC DRUGS

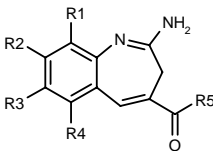
262091

2-Amino-8-hydroxy-9-methoxy-3*H*-1-benzazepine-4-carboxylic acid ethyl ester



C14-H16-N2-O4; Mol wt: 276.29

ACTION – Immunosuppressant for the treatment of myelosuppression including that associated with cancer chemotherapy, and for the prevention and treatment of viral, fungal, bacterial and parasitic infections. It appears to act by stimulating the production of granulocyte or granulocyte–macrophage colony-stimulating factor (G-CSF or GM-CSF). Other specifically claimed 2-aminobenzazepine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
262883	OMe	H	H	H	OEt	C ₁₄ H ₁₆ N ₂ O ₃
262884	H	OMe	OH	H	OEt	C ₁₄ H ₁₆ N ₂ O ₄
262885	H	H	H	OMe	OEt	C ₁₄ H ₁₆ N ₂ O ₃
262886	H	Ac	H	H	OEt	C ₁₅ H ₁₆ N ₂ O ₃
262887	H	Ac	H	H	N(Pr) ₂	C ₁₉ H ₂₆ N ₃ O ₂
262888	H	OH	OMe	H	OEt	C ₁₄ H ₁₆ N ₂ O ₄
262889	H	H	H	H	NHCH(Me)CO ₂ Me	C ₁₅ H ₁₇ N ₃ O ₃
262890	H	H	H	H	NHCH(Me)CO ₂ CH ₂ Ph	C ₂₁ H ₂₁ N ₃ O ₃
262891	H	H	H	H	NHCH(i-Pr)CO ₂ Me	C ₁₇ H ₂₁ N ₃ O ₃
262892	H	H	H	H	H	C ₁₁ H ₁₀ N ₂ O

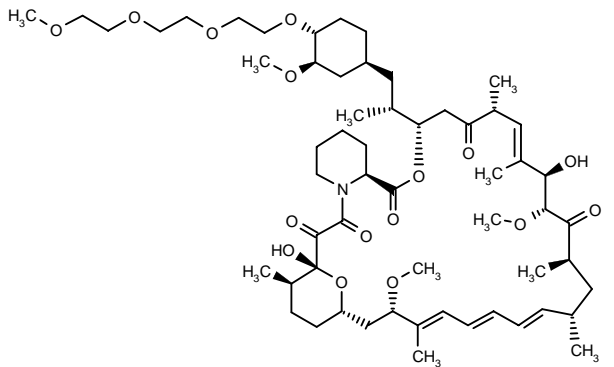
SOURCE – Pfizer.

REFERENCES

1. Cooper, C.B. et al. (Pfizer, Inc.) *2-Aminobenzazepine derivs. and their use for the treatment of immunosuppression*. EP 825186, JP 98087631.

263808

[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*R*)],15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-12-[2-[3-methoxy-4-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-cyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

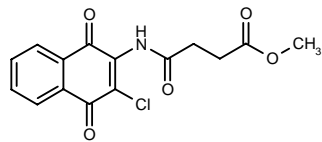


C58-H93-N-O16; Mol wt: 1060.37

PP1D-1

262043

N-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-succinamic acid methyl ester



C15-H12-Cl-N-O5; Mol wt: 321.72

M.p. 174-5 °C.

ACTION – Antiinflammatory and antiallergic agent and platelet aggregation inhibitor shown to inhibit the aggregation of rabbit platelets induced by thrombin, PAF, collagen, arachidonic acid and U-46619 with IC₅₀ values of 17.9, 9.8, 3.9, 1.8 and 1.7 μM, respectively, and also to inhibit ATP release from stimulated platelets; compound did not affect cyclooxygenase and thromboxane synthase activities, but appeared to exert its antiplatelet effects mainly by inhibiting phosphoinositide turnover. It also displays *in vitro* antiinflammatory (inhibition of β-glucuronidase and lysozyme release from neutrophils at 0.1-1 μg/ml and of superoxide formation at 0.3-1 μg/ml) and antiallergic activity (inhibition of β-glucuronidase and histamine release from mast cells at 0.1-1 μg/ml). *In vivo*, it inhibited polymyxin B-induced paw edema in mice and ear edema caused by several agents after i.p. or p.o. administration, which was suggested to involve protection of the microvasculature against inflammatory mediators.

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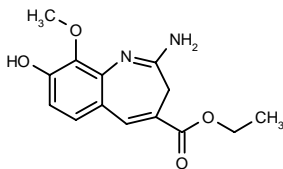
3. Lien, J.-C. et al. *Synthesis and antiplatelet, antiinflammatory, and antiallergic activities of 2-substituted 3-chloro-1,4-naphthoquinone derivatives*. Bioorg Med Chem 1997, 5(12): 2111.

4. Wang, J.P. et al. *Inhibition of hind-paw edema and cutaneous vascular plasma extravasation by 2-chloro-3-methoxycarbonylpropionamido-1,4-naphthoquinone (PP1D1) in mice*. Naunyn-Schmied Arch Pharmacol 1996, 354(6): 779.

IMMUNOLOGIC DRUGS

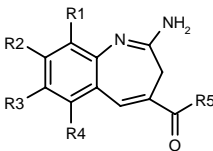
262091

2-Amino-8-hydroxy-9-methoxy-3*H*-1-benzazepine-4-carboxylic acid ethyl ester



C14-H16-N2-O4; Mol wt: 276.29

ACTION – Immunosuppressant for the treatment of myelosuppression including that associated with cancer chemotherapy, and for the prevention and treatment of viral, fungal, bacterial and parasitic infections. It appears to act by stimulating the production of granulocyte or granulocyte–macrophage colony-stimulating factor (G-CSF or GM-CSF). Other specifically claimed 2-aminobenzazepine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
262883	OMe	H	H	H	OEt	C ₁₄ H ₁₆ N ₂ O ₃
262884	H	OMe	OH	H	OEt	C ₁₄ H ₁₆ N ₂ O ₄
262885	H	H	H	OMe	OEt	C ₁₄ H ₁₆ N ₂ O ₃
262886	H	Ac	H	H	OEt	C ₁₅ H ₁₆ N ₂ O ₃
262887	H	Ac	H	H	N(Pr)2	C ₁₉ H ₂₆ N ₃ O ₂
262888	H	OH	OMe	H	OEt	C ₁₄ H ₁₆ N ₂ O ₄
262889	H	H	H	H	NHCH(Me)CO2Me	C ₁₅ H ₁₇ N ₃ O ₃
262890	H	H	H	H	NHCH(Me)CO2CH2Ph	C ₂₁ H ₂₁ N ₃ O ₃
262891	H	H	H	H	NHCH(i-Pr)CO2Me	C ₁₇ H ₂₁ N ₃ O ₃
262892	H	H	H	H	H	C ₁₁ H ₁₀ N ₂ O

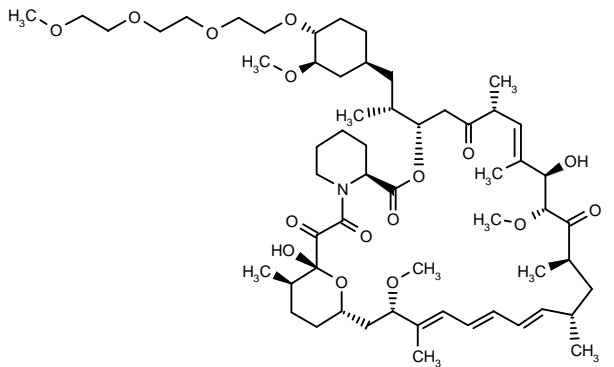
SOURCE – Pfizer.

REFERENCES

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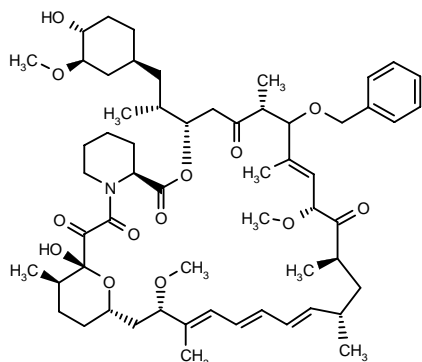
263808

[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*R*)],15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-12-[2-[3-methoxy-4-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-cyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

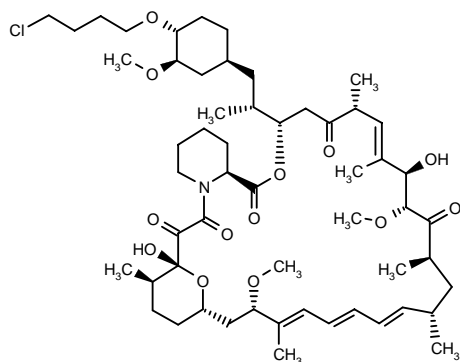


C58-H93-N-O16; Mol wt: 1060.37

ACTION – Rapamycin (sirolimus) analog with immuno-suppressive activity, as demonstrated by the ability to inhibit comitogen-induced murine thymocyte proliferation ($IC_{50} = 1.47 \mu M$) and to prolong survival time of pinch skin grafts from male DBA/2 donors transplanted to male BALB/c recipients. Antiinflammatory activity was demonstrated in the rat adjuvant arthritis model at 2 mg/kg p.o. Claimed for use in the treatment of transplant rejection, graft-vs.-host disease, asthma, rheumatoid arthritis, fungal infections, restenosis and cancer. Other specifically claimed compounds from this series of alkylated rapamycin derivatives include the following:



264693: C58-H85-N-O13



264694: C55-H86-Cl-N-O13

SOURCE – American Home Products.

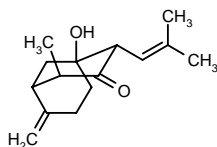
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1. Hu, D.C. et al. (American Home Prods. Corp.) Alkylated rapamycin derivs. WO 9809970.

AM-6898A

259186

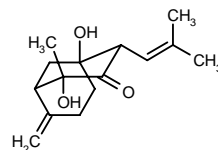
(1*R*,2*S*,4*S*,5*R*)-1-Hydroxy-4-methyl-6-methylene-2-(2-methyl-1-propenyl)bicyclo[3.3.1]nonan-3-one



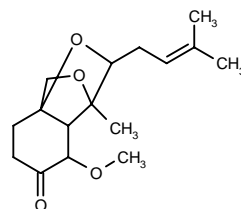
C15-H22-O2; Mol wt: 234.34

ACTION – Immunosuppressant isolated from *Pseudallescheria ellipsoideum* M6898 (FERM BP-5543), proven to inhibit IgE production in spleen cells of

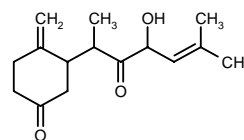
sensitized mice stimulated with lipopolysaccharide (LPS) and IL-4 ($IC_{50} = 0.00012 \mu g/ml$), with a negligible inhibitory effect on IgG_{2b} production. Other compounds from this source include the following:



AM-6898B [263535]: C15-H22-O3



AM-6898C [263536]: C16-H24-O4



AM-6898D [263537]: C15-H22-O3

SOURCE – Asahi Chem.

REFERENCES

1. Yaginuma, S. and Ishikawa, S. (Asahi Chem. Ind. Co., Ltd.) Novel cpd. AM6898 and preparation method thereof. JP 97309859.

BASILIXIMAB

Prop INN

235373

A chimeric CD25 monoclonal antibody constructed from the murine hybridoma RFT5γ2a and chimerized with human IgG_{1κ} that reacts with the IL-2 receptor α-chain

Immunoglobulin G₁ (human–mouse monoclonal CHI621 heavy chain anti-human interleukin-2 receptor), disulfide with human–mouse monoclonal CHI621 light chain, dimer

CHI-621⁺

chRFT5

SDZ-CHI-621

ACTION – Immunosuppressant, a murine/human chimeric monoclonal antibody directed against the IL-2 receptor α-chain (CD25 antigen) expressed on the surface of T-lymphocytes in response to antigenic challenge. It specifically binds to the CD25 antigen on activated T-lymphocytes expressing the high-affinity IL-2 receptor, thereby preventing IL-2 binding and subsequent T-cell proliferation.

INDICATION – Prophylaxis of acute organ rejection in *de novo* renal transplantation in combination with ciclosporin and corticosteroid-based immunosuppression.

PRESENTATION – Vials containing lyophilized powder, 20 mg, plus a solvent ampule containing 5 ml water for injection.

PROPRIETARY NAME – Simulect (CH).

SOURCE – Novartis.

RECENT REFERENCES

1. Breidenbach, T. et al. *Pharmacokinetic and pharmacodynamic evaluations of basiliximab (Simulect™) in a phase I/II trial in liver transplanted patients.* 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 64.

2. Breidenbach, T. et al. *Single centre results of a phase III trial with basiliximab (Simulect™) in kidney transplanted patients.* 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 123.

3. Kahan, B.D. et al. *Reduction of acute cellular rejection in renal allograft patients with basiliximab (Simulect™).* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 704.

4. Kahan, B.D. et al. *Reduction of acute cellular rejection in renal allograft patients with basiliximab (Simulect™).* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 43.

5. Kovarik, J. et al. *Pharmacokinetics of Simulect in recipients of cadaver kidney transplants.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 360.

6. Kovarik, J. et al. *Pharmacokinetics and immunodynamics of Simulect in liver transplant recipients.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 236.

7. Kovarik, J. et al. *Pharmacokinetics of basiliximab (Simulect™) in renal allograft patients.* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 370.

8. Kovarik, J. et al. *Disposition of basiliximab, an interleukin-2 receptor monoclonal antibody, in recipients of mismatched cadaver renal allografts.* Transplantation 1997, 64(12): 1701.

9. Nashan, B. et al. *Immunoprophylaxis with a chimeric anti-IL-2R monoclonal antibody in liver transplanted patients.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 77.

10. Nashan, B. et al. *Reduction of acute cellular rejection by basiliximab (Simulect™), in renal allograft recipients.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 705.

11. Nashan, B. et al. *Reduction of acute cellular rejection by basiliximab (Simulect™), an anti-IL-2R MAb, in renal allograft recipients.* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 42.

12. Nashan, B. et al. *Immunoprophylaxis with a chimeric anti-IL-2R monoclonal antibody (Simulect®) in liver transplanted patients.* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 369.

13. Nashan, B. et al. *Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients.* Lancet 1997, 350(9086): 1193.

14. Nashan, B. *Reduction of acute cellular rejection by basiliximab (Simulect™), in renal allograft recipients.* Jpn J Transplant 1997, 32: Abst S-2-4.

15. *Basiliximab launch.* Novartis Pharmaceutical, Inc. Company Communication 1998, May 11.

16. *FDA clears Novartis to market Simulect for use in renal transplantation.* Prous Science Daily Essentials May 14, 1998.

17. *First marketing approval for Novartis transplant drug.* Prous Science Daily Essentials April 22, 1998.

18. *First market introduction for basiliximab.* Prous Science Daily Essentials May 12, 1998.

19. *Novartis' new transplantation drug Simulect® gets first market approval.* Novartis Pharmaceutical, Inc. Press Release 1998, April 15.

20. *Novartis submits BLA for Simulect in U.S.* Prous Science Daily Essentials November 17, 1997.

MONOGRAPH – Graul, A. et al. *Basiliximab.* Drugs Fut 1998, 23(8): in preparation.

*Drug Data Rep 1996, 18(7): 647.

PNCRM7

261651

Heptavalent pneumococcal vaccine composed of polysaccharides of serotypes 4, 6B, 9V, 14, 19F, 23F and oligosaccharides of 18C, in which each serotype is independently coupled to CRM₁₉₇ via reductive amination and combined into the 7-valent formulation

ACTION – Heptavalent pneumococcal vaccine that has been proven safe and effective in children when administered at 2, 4, 6 and 12-15 months of age and to significantly increase specific antibodies against the 7 pneumococcal strains included in the vaccine. After 3 doses of PNCRM7, 92-100% of children had 0.15 µg/ml or more of antibody, and 51-90% had levels of 1 µg/ml or more, and a booster dose produced an anamnestic response to all 7 vaccine serotypes. The vaccine may be useful for protecting children against pneumococcal diseases such as otitis media, bacteremia and bacterial meningitis.

SOURCES – Wyeth-Lederle Vaccines and Pediatrics.

REFERENCES

1. Rennels, M.B. et al. *Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.* Pediatrics 1998, 101(4): 604.

2. *Vaccine against pneumococcal disease shown safe and immunogenic in children.* Prous Science Daily Essentials April 14, 1998.

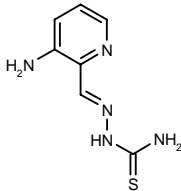
ONCOLYTIC DRUGS

ANTIMETABOLITES

3-AP*

205299

3-Aminopyridine-2-carboxaldehyde thiosemicarbazone



C7-H9-N5-S; Mol wt: 195.24

PROPRIETARY NAME – Simulect (CH).

SOURCE – Novartis.

RECENT REFERENCES

1. Breidenbach, T. et al. *Pharmacokinetic and pharmacodynamic evaluations of basiliximab (Simulect™) in a phase I/II trial in liver transplanted patients.* 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 64.

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3. Kahan, B.D. et al. *Reduction of acute cellular rejection in renal allograft patients with basiliximab (Simulect™).* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 704.

4. Kahan, B.D. et al. *Reduction of acute cellular rejection in renal allograft patients with basiliximab (Simulect™).* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 43.

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6. Kovarik, J. et al. *Pharmacokinetics and immunodynamics of Simulect in liver transplant recipients.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 236.

7. Kovarik, J. et al. *Pharmacokinetics of basiliximab (Simulect™) in renal allograft patients.* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 370.

8. Kovarik, J. et al. *Disposition of basiliximab, an interleukin-2 receptor monoclonal antibody, in recipients of mismatched cadaver renal allografts.* Transplantation 1997, 64(12): 1701.

9. Nashan, B. et al. *Immunoprophylaxis with a chimeric anti-IL-2R monoclonal antibody in liver transplanted patients.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 77.

10. Nashan, B. et al. *Reduction of acute cellular rejection by basiliximab (Simulect™), in renal allograft recipients.* 16th Annu Meet Sci Sess Bus Meet Amer Soc Transplant Physicians (May 10-14, Chicago) 1997, Abst 705.

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12. Nashan, B. et al. *Immunoprophylaxis with a chimeric anti-IL-2R monoclonal antibody (Simulect®) in liver transplanted patients.* 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 369.

13. Nashan, B. et al. *Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients.* Lancet 1997, 350(9086): 1193.

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15. *Basiliximab launch.* Novartis Pharmaceutical, Inc. Company Communication 1998, May 11.

16. *FDA clears Novartis to market Simulect for use in renal transplantation.* Prous Science Daily Essentials May 14, 1998.

17. *First marketing approval for Novartis transplant drug.* Prous Science Daily Essentials April 22, 1998.

18. *First market introduction for basiliximab.* Prous Science Daily Essentials May 12, 1998.

19. *Novartis' new transplantation drug Simulect® gets first market approval.* Novartis Pharmaceutical, Inc. Press Release 1998, April 15.

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MONOGRAPH – Graul, A. et al. *Basiliximab.* Drugs Fut 1998, 23(8): in preparation.

*Drug Data Rep 1996, 18(7): 647.

PNCRM7

261651

Heptavalent pneumococcal vaccine composed of polysaccharides of serotypes 4, 6B, 9V, 14, 19F, 23F and oligosaccharides of 18C, in which each serotype is independently coupled to CRM₁₉₇ via reductive amination and combined into the 7-valent formulation

ACTION – Heptavalent pneumococcal vaccine that has been proven safe and effective in children when administered at 2, 4, 6 and 12-15 months of age and to significantly increase specific antibodies against the 7 pneumococcal strains included in the vaccine. After 3 doses of PNCRM7, 92-100% of children had 0.15 µg/ml or more of antibody, and 51-90% had levels of 1 µg/ml or more, and a booster dose produced an anamnestic response to all 7 vaccine serotypes. The vaccine may be useful for protecting children against pneumococcal diseases such as otitis media, bacteremia and bacterial meningitis.

SOURCES – Wyeth-Lederle Vaccines and Pediatrics.

REFERENCES

1. Rennels, M.B. et al. *Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.* Pediatrics 1998, 101(4): 604.

2. *Vaccine against pneumococcal disease shown safe and immunogenic in children.* Prous Science Daily Essentials April 14, 1998.

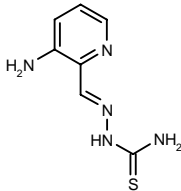
ONCOLYTIC DRUGS

ANTIMETABOLITES

3-AP*

205299

3-Aminopyridine-2-carboxaldehyde thiosemicarbazone



C7-H9-N5-S; Mol wt: 195.24

ACTION – Antineoplastic agent that acts by inhibiting ribonucleotide reductase (ribonucleoside-diphosphate reductase). It is effective *in vitro* against cultured wild-type L1210 and hydroxyurea-resistant L1210 cell lines (IC_{50} = 1.3 and 1.6 μ M, respectively), which is correlated with its inhibitory effect on CDP reductase (IC_{50} = 0.3 μ M). Studies *in vivo* showed that 3-AP (40 mg/kg/day i.p. x 6 days or 10-30 mg/kg b.i.d. i.p. x 6 days) significantly increased survival time in mice bearing L1210 leukemia (T/C x 100 = 187 and 96-262%, respectively), with 4 of 10 long-term survivors (> 60 days) at 10 mg/kg b.i.d. i.p. x 6. Antitumor activity was also observed in mice bearing murine lung carcinoma M109 and human ovarian carcinoma A2780 xenografts. Combination of 3-AP and DNA-damaging agents (e.g., etoposide, cisplatin) resulted in a synergistic inhibition of L1210 leukemia.

SOURCES – Vion; Yale Univ. School Med., New Haven, CT (US).

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1. Sartorelli, A.C. and Lin, T.-S. (Yale Univ.) 2-Formylpyridine thiosemicarbazone derivs., their preparation and their use as antitumor agents. EP 570294, JP 94128230, US 5281715, US 5721259.
2. Cory, J.G. et al. Inhibitors of ribonucleotide reductase: Comparative effects of amino- and hydroxy-substituted pyridine-2-carboxaldehyde thiosemicarbazones. *Biochem Pharmacol* 1994, 48(2): 335.
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5. Liu, M.-C. et al. Synthesis and antitumor activity of amino derivatives of pyridine-2-carboxaldehyde thiosemicarbazone. *J Med Chem* 1992, 35(20): 3672.
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7. Vion Pharmaceuticals reports fourth quarter and year end financial results. Vion Pharmaceuticals, Inc. Press Release 1996, February 22.
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*Identified compound **205299** (see **203855**) Drug Data Rep 1994, 16(3): 301.

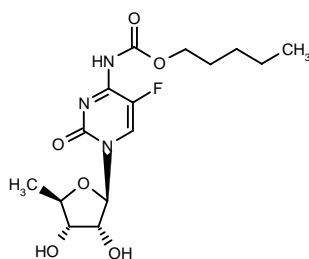
CAPECITABINE⁺

Rec INN; USAN

211639

N-[1-(5-Deoxy- β -D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamic acid pentyl ester

Ro-09-1978



C15-H22-F-N3-O6; Mol wt: 359.35

ACTION – Oral tumor-activated antineoplastic agent, an oral prodrug of 5'-DFUR (5'-deoxy-5-fluorouridine) that is converted *in vivo* to 5-fluorouracil (5-FU).

INDICATION – Treatment of metastatic breast cancer in patients whose tumors are resistant to standard chemotherapy with paclitaxel and an anthracycline-containing regimen.

PRESENTATION – Tablets, 150 and 500 mg.

PROPRIETARY NAME – *Xeloda* (US).

SOURCE – Roche.

RECENT REFERENCES

1. Blum, J.L. et al. A multicenter phase II trial of *Xeloda*TM (capecitabine) in paclitaxel-refractory metastatic breast cancer (MBC). *Proc Amer Soc Clin Oncol* 1998, 17: Abst 476.
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5. Gliesche, R. et al. Relationships between metrics of exposure to *Xeloda*TM and occurrence of adverse effects. *Proc Amer Soc Clin Oncol* 1998, 17: Abst 861.
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11. Khoury, P. et al. Phase I study of capecitabine in combination with paclitaxel in patients with previously treated metastatic breast cancer. *Proc Amer Soc Clin Oncol* 1998, 17: Abst 793.
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14. Pronk, L. et al. A matrix-designed phase I dose-finding and pharmacokinetic study of the combination of *Xeloda*TM plus *Taxotere*TM. *Proc Amer Soc Clin Oncol* 1998, 17: Abst 816.
15. Reigner, B. et al. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998, 4(4): 941.
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17. Schüller, J. et al. Tumor selectivity of *Xeloda*TM in colorectal cancer patients. *Proc Amer Soc Clin Oncol* 1997, 16: Abst 797.
18. *Capecitabine clinical data and product introduction announced at ASCO*. Prous Science Daily Essentials May 22, 1998.
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20. *Data presented at ASCO for new oral breast cancer drug that received FDA accelerated approval*. Roche Press Release 1998, May 19.

21. *FDA advisory committee recommends approval of capecitabine*. Prous Science Daily Essentials March 23, 1998.

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23. *FDA grants accelerated approval for Xeloda™, the first oral chemotherapy for the treatment of patients with metastatic breast cancer resistant to standard chemotherapies*. Roche Press Release 1998, April 30.

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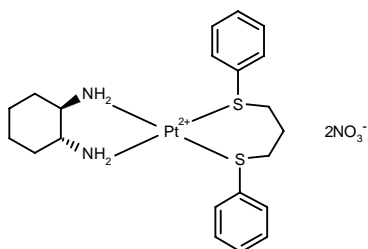
*Drug Data Rep 1995, 17(11): 1045.

DNA-DAMAGING DRUGS

KHPC-10

261785

[1,3-Bis(phenylsulfanyl)propane- $\kappa S^1, S^3$][*trans-l*-(1,4-diaminocyclohexane- $\kappa N^1, N^4$)]platinum(II) dinitrate



C21-H30-N4-O6-Pt-S2; Mol wt: 693.70

ACTION – Antineoplastic platinum(II) complex with at least comparable activity to cisplatin against murine leukemia L1210, human prostate cancer DU-145 and human bladder cancer HT-1376 cells. However, it produced much less renal toxicity than cisplatin in cytotoxic assays in rabbit and human tissues.

SOURCE – Kyung Hee Univ., Seoul (KR).

REFERENCES

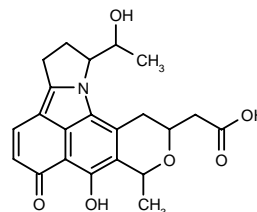
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ANTIBIOTICS AND ALKALOIDS

BE-54238A

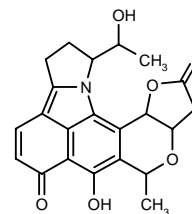
262806

2-[7-Hydroxy-1-(1-hydroxyethyl)-8-methyl-6-oxo-2,3,6,8,10,11-hexahydro-1*H*-benzo[*cd*]pyrano[3,4-*g*]-pyrrolo[1,2-*a*]indol-10-yl]acetic acid



C22-H23-N-O6; Mol wt: 397.43

ACTION – Antineoplastic agent produced by culturing the microorganism *Streptomyces* sp. A54238 (FERM P-15721), with *in vitro* cytotoxicity against murine P388 leukemia, murine colon 26, human colon cancer DLD-1, human lung cancer PC-13 and human gastric cancer MKN-45 cells (IC_{50} = 3.6, 3.4, 1.4, 4.5 and 3.2 μ g/ml, respectively). Another related compound is:



BE-54238B [263068]: C22-H21-N-O6

SOURCE – Banyu.

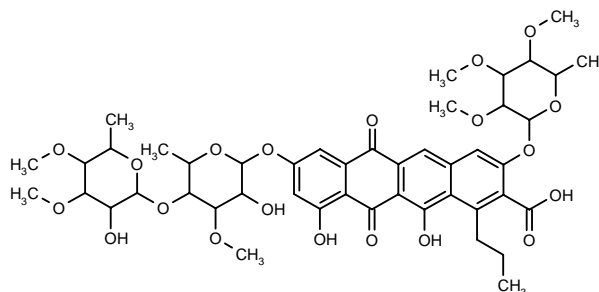
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BE-56980

262812

10,12-Dihydroxy-8-[3-hydroxy-5-(3-hydroxy-4,5-dimethoxy-6-methyltetrahydropyran-2-yloxy)-4-methoxy-6-methyltetrahydropyran-2-yloxy]-6,11-dioxo-1-propyl-3-(3,4,5-trimethoxy-6-methyltetrahydropyran-2-yloxy)-6,11-dihydronaphthacene-2-carboxylic acid



C46-H58-O20; Mol wt: 930.95

ACTION – Antineoplastic agent isolated from a culture of *Actinoplanes* sp. A56980 (FERM P-15716), with *in vitro* cytotoxicity against murine colon 26, human colon cancer DLD-1, human lung cancer PC-13 and human gastric cancer MKN-45 cells (IC₅₀ = 2.4, 4.3, 7.3 and 4.4 µg/ml, respectively).

SOURCE – Banyu.

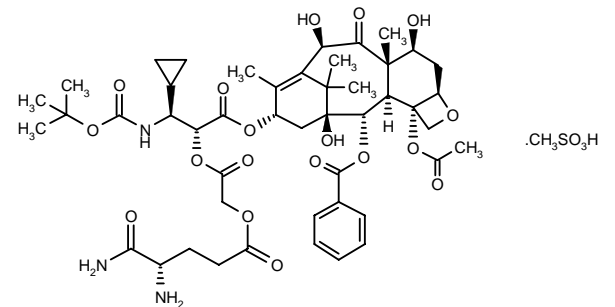
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ANTIMITOTIC DRUGS

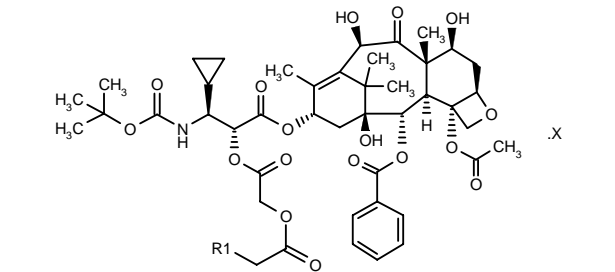
261865

[2a*R*]-[2aα,4β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12aα,12bα]]-12b-Acetoxy-9-[2(*R*)-[2-[4(*S*)-amino-4-carbamoyl-butyryloxy]acetoxy]-3(*S*)-(tert-butoxycarbonylamino)-3-cyclopropylpropionyloxy]-12-(benzyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methano-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one methanesulfonate



C47-H63-N3-O18.C-H4-O3-S; Mol wt: 1054.12

ACTION – Antineoplastic agent found to prolong survival time in mice bearing melanoma B16, with a 214.9% increase in life span at a dose 6.3 mg/kg/day x 5 days i.v. Other representative compounds within this series of baccatin derivatives include the following:



Compound	R1	R2	Formula
262774	(S)-CH(NH2)CONH2	MeSO3H	C ₄₆ H ₆₁ N ₃ O ₁₈ .CH ₄ O ₃ S
262777	(S)-CH2CH(NH2)CO2Et	MeSO3H	C ₄₉ H ₆₆ N ₂ O ₁₉ .CH ₄ O ₃ S
262778	(S)-CH(NH2)CONHMe	MeSO3H	C ₄₇ H ₆₃ N ₃ O ₁₈ .CH ₄ O ₃ S
262779	(R)-CH(NH2)CONH2	MeSO3H	C ₄₆ H ₆₁ N ₃ O ₁₈ .CH ₄ O ₃ S
262780	(S)-CH(NH2)CONH2	tosylate	C ₄₆ H ₆₁ N ₃ O ₁₈ .C ₇ H ₆ O ₃ S

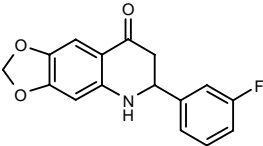
SOURCE – Tanabe Seiyaku.

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1. Tsujihara, K. et al. (Tanabe Seiyaku Co., Ltd.) *Medicinal compsns*. JP 98045583.

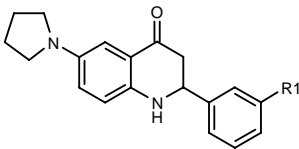
262987

6-(3-Fluorophenyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]-quinolin-8-one



C16-H12-F-N-O3; Mol wt: 285.27

ACTION – Antimitotic antineoplastic agent proven to inhibit tubulin polymerization (IC₅₀ = 0.75 ± 0.04 µM) with cytotoxicity against a range of human tumor cell lines such as ileocecal carcinoma HCT-8, breast cancer MCF-7, lung carcinoma A-549, epidermoid carcinoma KB, renal cancer CAKI-1 and melanoma SKMEL-2 cells (ED₅₀ = 0.012-0.032 µg/ml). Other 2',3',4',6,7-substituted 2,3-dihydro-2-aryl-4(1*H*)-quinolone derivatives include the following:



Compound	R1	Formula
262988	OMe	C ₂₀ H ₂₂ N ₂ O ₂
262989	Cl	C ₁₉ H ₁₉ ClN ₂ O

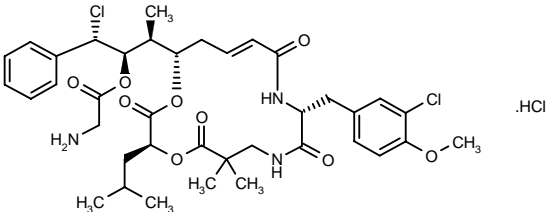
SOURCES – Natl. Cancer Inst., Frederick Cancer Res. Dev. Cent., Frederick, MD (US); Univ. North Carolina Chapel Hill, Chapel Hill, NC (US).

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1. Xia, Y. et al. *Antitumor agents. 181. Synthesis and biological evaluation of 6,7,2',3',4'-substituted-1,2,3,4-tetrahydro-2-phenyl-4-quinolones as a new class of antimitotic antitumor agents*. J Med Chem 1998, 41(7): 1155.

263323

[3*S*-(3α,10β,13*E*,16β)]-16-[2(*R*)-(2-Aminoacetoxy)-3(*S*)-chloro-1(*S*)-methyl-3-phenylpropyl]-10-(3-chloro-4-methoxybenzyl)-3-isobutyl-6,6-dimethyl-1,4-dioxo-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetraone hydrochloride



C38-H49-Cl2-N3-O9.HCl; Mol wt: 799.19

ACTION – Antineoplastic agent that exerts its action by disrupting the microtubulin system and shows good aqueous solubility and stability. It was tested *in vitro* in the human colon carcinoma GC3 screen, giving an IC_{50} of 0.10 nM.

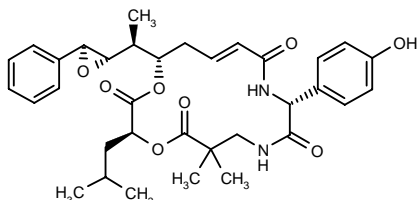
SOURCES – Univ. Hawaii, Honolulu, HI (US); Lilly; Wayne State Univ., Detroit, MI (US).

REFERENCES

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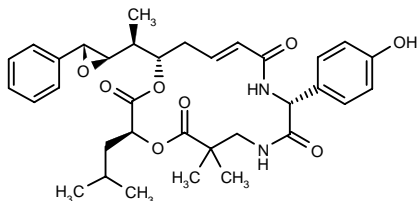
263324

(3*S*,10*R*,13*E*,16*S*)-16-[2(*R*),3(*S*)-Epoxy-1(*S*)-methyl-3-phenylpropyl]-10-(4-hydroxyphenyl)-3-isobutyl-6,6-dimethyl-1,4-dioxo-8,11-diaza-13-cyclohexadecene-2,5,9,12-tetraone



C34-H42-N2-O8; Mol wt: 606.71

ACTION – Antineoplastic agent that acts by disrupting the microtubule system, reported to possess improved solubility over related compounds. Compound is also reported to possess antifungal activity. Another compound from this series of cryptophycin derivatives is:



264318: C34-H42-N2-O8

SOURCES – Univ. Hawaii, Honolulu, HI (US); Lilly; Wayne State Univ., Detroit, MI (US).

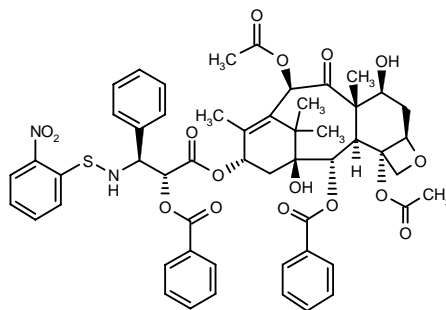
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1. Al-Awar, R.S. et al. (Eli Lilly & Co.; Univ. Hawaii; Wayne State Univ.) *Pharmaceutical cpds.* WO 9808506.

BMS-200659

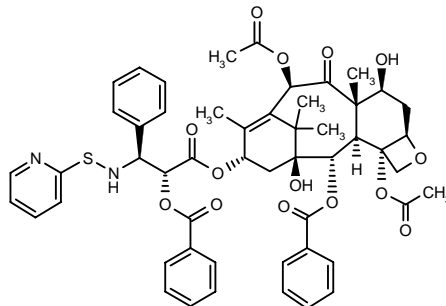
263353

[2*aR*]-[2*a* α ,4 β ,4*a* β ,6 β ,9 α (2*R*,3*S*),11 β ,12*a* α ,12*ba*]]-6,12*b*-Diacetoxy-12-benzoyloxy-9-[2-benzoyloxy-3-(2-nitrophenylsulfanyl)-3-phenylpropionyloxy]-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2- β]oxet-5-one



C53-H54-N2-O16-S; Mol wt: 1007.07

ACTION – Antineoplastic agent shown to prolong survival time of mice bearing lung carcinoma M109 tumors, giving a T/C value of 156% at 32 mg/kg i.v. on days 4-8 vs. 227% for paclitaxel at 24 mg/kg i.v. on days 4-8; when the compound was administered i.p. on days 5 and 8, it gave a T/C value of 148% at 100 mg/kg vs. 145% for paclitaxel at 60 mg/kg. Another compound from this series of sulfenamide taxane derivatives is:



BMS-200274 [264544]: C52-H54-N2-O14-S

SOURCE – Bristol-Myers Squibb.

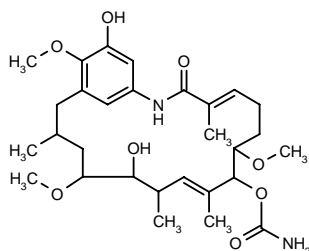
REFERENCES

1. Scola, P.M. and Vyas, D.M. (Bristol-Myers Squibb Co.) *Sulfenamide taxane derivs.* WO 9808833.

REBLASTATIN

258412

9-(Carbamoyloxy)-13,20-dihydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-2-azabicyclo[16.3.1]docosa-1(22),4(E),10(E),18,20-pentaen-3-one



C29-H44-N2-O8; Mol wt: 548.68

ACTION – Antineoplastic agent isolated from *Streptomyces hygroscopicus* subsp. *hygroscopicus* SANK 61995 (FERM BP-5140) that acts by arresting the cell cycle at G1, as demonstrated *in vitro* using human lung cancer A549 cells. Compound was shown to inhibit the proliferation of A549 cells with an IC₅₀ value of 1.5 µg/ml.

SOURCE – Sankyo.

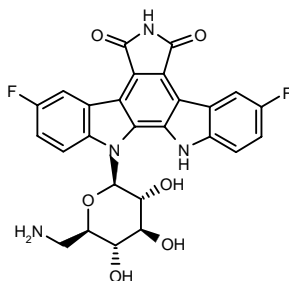
REFERENCES

1. Takatsu, T. et al. (Sankyo Co., Ltd.) *Novel reblastatin cpds.* JP 97286779.

DNA-INTERCALATING DRUGS

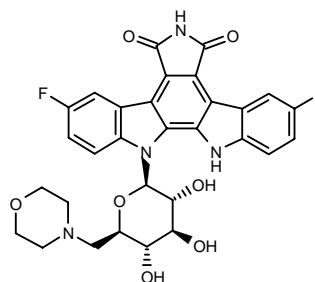
263283

12-(6-Amino-6-deoxy-β-D-glucopyranosyl)-3,9-difluoro-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]-carbazole-5,7-dione



C26-H20-F2-N4-O6; Mol wt: 522.46

ACTION – Antineoplastic agent with topoisomerase I-inhibitory activity, as demonstrated by an EC₅₀ value of 0.04 µM for inducing human purified topoisomerase I-mediated single-strand break formation in marine bacteriophage PM2 DNA. Compound inhibited the proliferation of human colon carcinoma HCT116 cells with an IC₅₀ value of 0.11 µM and was shown to prolong survival time of mice bearing P388 leukemia (T/C x 100 = 182 and 155%, respectively, at 100 and 25 mg/kg i.p.). Another compound from this series of amino sugar derivatives of indolopyrrolocarbazoles is:



264028: C30-H26-F2-N4-O7

SOURCE – Bristol-Myers Squibb.

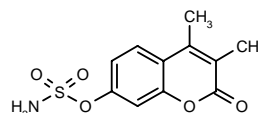
REFERENCES

1. Saulnier, M.G. et al. (Bristol-Myers Squibb Co.) *Cytotoxic amino sugar and related sugar derivs. of indolpyrrolocarbazoles.* WO 9807433.

HORMONAL AGENTS

262976

Sulfamic acid 3,4-dimethyl-2-oxo-2H-1-benzopyran-7-yl ester



C11-H11-N-O5-S; Mol wt: 269.27

White crystals, m.p. 194-6 °C.

ACTION – Agent for the treatment of hormone-dependent breast cancer, a nonestrogenic, sulfamate-based inhibitor of the enzyme steroid sulfatase, as shown in intact human breast cancer MCF-7 cells (IC₅₀ = 30 nM) and in placental microsomes (88.2% inhibition at 1 µM).

SOURCE – Univ. Bath, Bath (GB).

REFERENCES

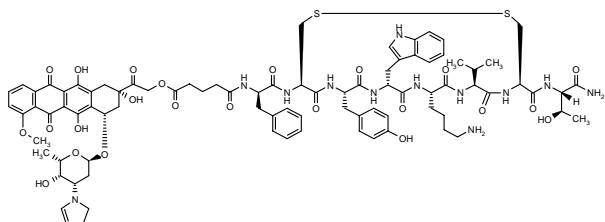
1. Woo, L.W.C. et al. *Steroidal and nonsteroidal sulfamates as potent inhibitors of steroid sulfatase.* J Med Chem 1998, 41(7): 1068.

AN-238

263091

N-[4-[3'-Desamino-3'-(2,3-dihydro-1*H*-pyrrol-1-yl)-adriamycin-14-*O*-yl]succinyl]-*D*-phenylalanyl-L-cysteinyl-L-tyrosyl-*D*-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide *S*-3.2-*S*-3.7-disulfide

N-[5-[2-[(2*S*,4*S*)-2,5,12-Trihydroxy-7-methoxy-6,11-dioxo-4-[2,3,6-trideoxy-3-(2,3-dihydro-1*H*-pyrrol-1-yl)- α -L-*Lyxo*-hexopyranosyloxy]-1,2,3,4,6,11-hexahydro-2-naphthacenyl]-2-oxoethoxy]-1,5-dioxopentyl]-*D*-phenylalanyl-L-cysteinyl-L-tyrosyl-*D*-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide cyclic (2 \rightarrow 7)-disulfide



C86-H104-N12-O23-S; Mol wt: 1737.95

ACTION – Hybrid somatostatin analog containing 2-pyrrolinodoxorubicin (AN-201) that exhibits cytotoxic and antiproliferative properties *in vitro* against a range of human cancer cell lines such as gastric MKN-45 (IC₅₀ = 0.36 nM), breast MDA-MB-231 (IC₅₀ = 0.32 nM), prostate PC-3 (IC₅₀ = 0.5 nM), pancreatic MIA PaCa-2 (IC₅₀ = 0.33 nM) and lung H-345 (IC₅₀ = 4.0 nM). It showed high affinity for somatostatin receptors (IC₅₀ = 23.8 nM for displacement of [¹²⁵I]-RC-160 in rat pituitary membranes) and also inhibited the pituitary release of growth hormone induced by hGH-RH(1-29)NH₂ (84-95% inhibition at 0.1-1 nM) or forskolin (54-70% inhibition at 0.5-2 nM). *In vivo* studies in animal models of breast and prostate cancers have shown that AN-238 administered i.v. is more effective and less toxic than AN-201, its cytotoxic radical constituent.

SOURCE – Asta Medica.

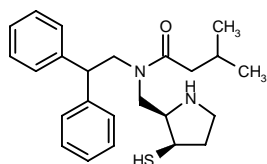
REFERENCES

- Schally, A.V. et al. (Asta Medica AG) *Targeted cytotoxic anthracycline analogs*. WO 9719954.
- Nagy, A. et al. *Synthesis and biological evaluation of cytotoxic analogs of somatostatin containing doxorubicin or its intensely potent derivative, 2-pyrrolinodoxorubicin*. Proc Natl Acad Sci USA 1998, 95(4): 1794.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

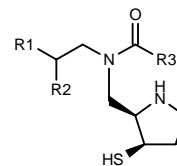
263289

cis-*N*-(2,2-Diphenylethyl)-3-methyl-*N*-(3-sulfanylpyrrolidin-2-ylmethyl)butyramide

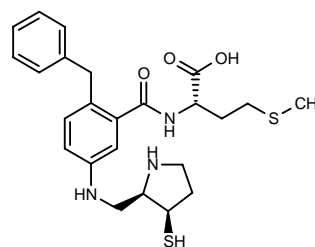


C24-H32-N2-O-S; Mol wt: 396.59

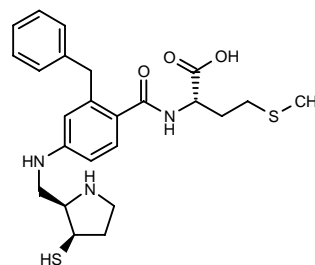
ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and Ras farnesylation. A representative compound from a series of specifically claimed 3-mercaptopyrrolidines, wherein the following are also included:



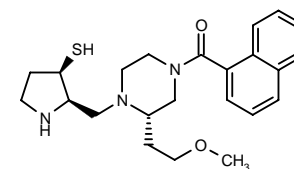
Compound	R1	R2	R3	Formula
264018	Ph	Ph	3-Pyr-CH ₂	C ₂₆ H ₂₉ N ₃ OS
264019	Ph	Ph	1-oxido-6-MeO-3-Pyr	C ₂₆ H ₂₉ N ₃ O ₃ S
264020	H	1-Naph	1-oxido-6-MeO-3-Pyr	C ₂₄ H ₂₇ N ₃ O ₃ S
264021	H	1-Naph	5-thiazolyl	C ₂₁ H ₂₃ N ₃ OS ₂



264022: C24-H31-N3-O3-S2



264023: C24-H31-N3-O3-S2



264024: C23-H31-N3-O2-S

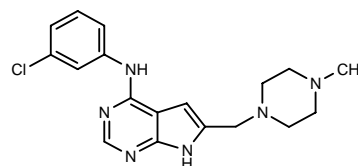
SOURCE – Zeneca.

REFERENCES

- Boyle, F.T. and Wardleworth, J.M. (Zeneca, Ltd.) *3-Mercaptopyrrolidines as farnesyl protein transferase inhibitors*. WO 9807692.

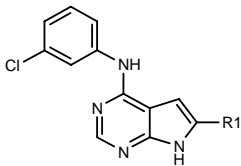
263307

4-(3-Chlorophenylamino)-6-(4-methylpiperazin-1-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine



C18-H21-Cl-N6; Mol wt: 356.86

ACTION – Antineoplastic agent, an inhibitor of tyrosine kinases such as epidermal growth factor (EGF) receptor protein tyrosine kinase and c-erbB2 kinase. A compound within a series of specifically claimed substituted pyrrolopyrimidines, wherein the following are also included:



Compound	R1	Formula
265052	4-morpholinyl-CH2	C ₁₇ H ₁₈ ClN ₅ O
265053	CH2N(CH2CH2OH)2	C ₁₇ H ₂₀ ClN ₅ O ₂
265054	4-MeO-PhCH2NHCH2	C ₂₁ H ₂₀ ClN ₅ O
265055	4-OH-PhCH2NHCH2	C ₂₀ H ₁₈ ClN ₅ O
265056	(E)-CH=NOH	C ₁₃ H ₁₀ ClN ₅ O
265057	(Z)-CH=NOH	C ₁₃ H ₁₀ ClN ₅ O
265058	CH=NOMe	C ₁₄ H ₁₂ ClN ₅ O
265059	4-morpholinyl-CO	C ₁₇ H ₁₆ ClN ₅ O ₂
265060	4-Me-1-Piz-CO	C ₁₈ H ₁₉ ClN ₅ O
265061	CSNH2	C ₁₃ H ₁₀ ClN ₅ S

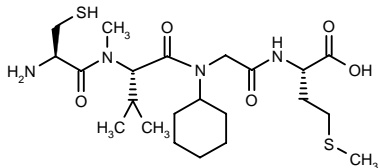
SOURCE – Novartis.

REFERENCES

1. Traxler, P. et al. (Novartis AG) *Subst. pyrrolopyrimidines and processes for their preparation*. WO 9807726.

263785

L-Cysteinyl-L-(N-methyl)valyl-(N-cyclohexyl)glycyl-L-methionine



C22-H40-N4-O5-S2; Mol wt: 504.70

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor derived from a farnesyltransferase universal recognition tetrapeptide sequence CAAX, with no effect on geranylgeranyltransferase.

SOURCE – Yissum.

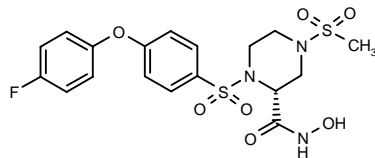
REFERENCES

1. Levitzki, A. et al. (Yissum Res. Develop. Co. Hebrew Univ. Jerusalem) *Semipeptoid farnesyl protein transferase inhibitors and analogs thereof*. WO 9809641.

ANTIANGIOGENIC AGENTS

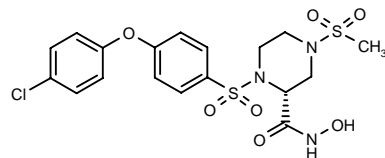
263739

1-[4-(4-Fluorophenoxy)phenylsulfonyl]-4-(methanesulfonyl)piperazine-2(R)-carboxydroxamic acid

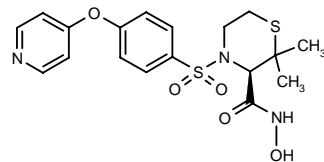


C18-H20-F-N3-O7-S2; Mol wt: 473.49

ACTION – Agent for controlling tumor growth, invasion or metastasis and for the treatment of arthritis, an inhibitor of matrix metalloproteinases and tumor necrosis factor- α (TNF- α) production. *In vitro*, it inhibited stromelysin, gelatinase and collagenase with K_i values of 0.130, 0.007 and 0.005 nM, respectively. *In vivo*, it was shown to inhibit lung metastases from Lewis lung carcinoma in mice by 77.6% relative to controls at 50 mg/kg/day i.p. x 21 days starting 24 h after tumor implantation, and also to delay primary tumor growth by 7.2 days relative to controls. Other specifically claimed compounds include the following:



263974: C18-H20-Cl-N3-O7-S2



263975: C18-H21-N3-O5-S2

SOURCE – Agouron.

REFERENCES

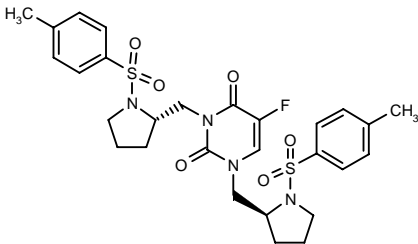
1. Bender, S.L. and Melnick, M.J. (Agouron Pharm., Inc.) *Metalloproteinase inhibitors, pharmaceutical compsns. containing them and their pharmaceutical uses*. US 5753653.

MISCELLANEOUS

ANTINEOPLASTIC AGENTS

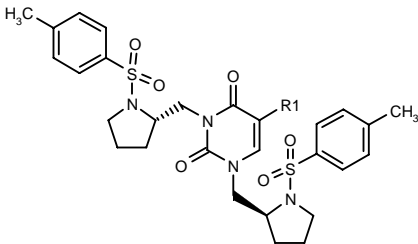
258413

5-Fluoro-1,3-bis[1-(4-methylphenylsulfonyl)pyrrolidin-2(S)-ylmethyl]uracil

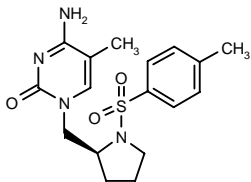


C28-H33-F-N4-O6-S2; Mol wt: 604.71

ACTION – Antineoplastic agent with potent cytotoxic activity against MT-4 cells (CC_{50} = 2.4 μ g/ml). Within this series of pyrimidine derivatives, the following are also included:



Compound	R1	Formula
263149	Me	C ₂₉ H ₃₆ N ₄ O ₆ S ₂
263150	Et	C ₃₀ H ₃₈ N ₄ O ₆ S ₂
263151	Br	C ₂₈ H ₃₃ BrN ₄ O ₆ S ₂



263152: C17-H22-N4-O3-S

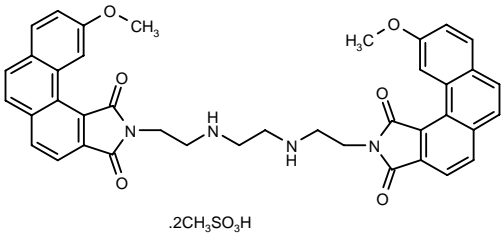
SOURCE – Nippon Paper.

REFERENCES

1. Kojima, E. et al. (Nippon Paper Ind. Co., Ltd.) *Pyrimidine derivs. and their use thereof as antitumor agents*. JP 97286786.

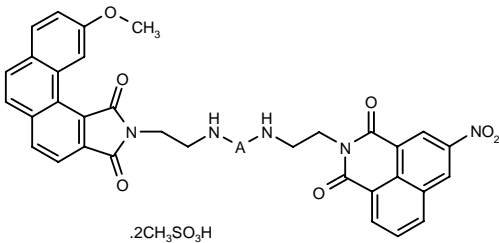
260879

2,2'-(3,6-Diazaoctane-1,8-diyl)bis(10-methoxy-2,3-dihydro-1*H*-naphtho[1,2-*e*]isoindole-1,3-dione) bismethane-sulfonate

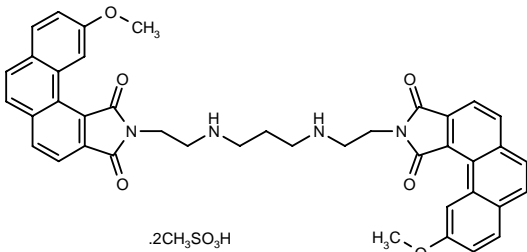


C40-H34-N4-O6.2C-H4-O3-S; Mol wt: 858.93

ACTION – Antineoplastic agent proven to inhibit tumor growth *in vivo* in nude mice bearing human epidermoid carcinoma KB-3-1 with a T/C x 100 of 26% at 15 mg/kg/day i.v. x 5 days. Other specifically claimed compounds from this series of bis-imide derivatives include the following:



Compound	A	Formula
263374	-(CH2)3-	C ₃₆ H ₃₁ N ₅ O ₇ .2CH ₄ O ₃ S
263375	-(CH2)2-	C ₃₅ H ₂₉ N ₅ O ₇ .2CH ₄ O ₃ S



263373: C41-H36-N4-O6.2CH4-O3-S

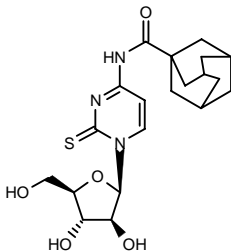
SOURCE – ADIR.

REFERENCES

1. Lavielle, G. et al. (ADIR et Cie.) *Bis imide derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 820985, JP 98067750.

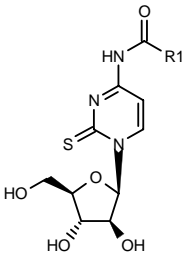
261857

*N*⁴-(Adamantan-1-ylcarbonyl)-1-(β-D-arabinofuranosyl)-2-thiocytosine



C20-H27-N3-O5-S; Mol wt: 421.51

ACTION – Antineoplastic agent proven to prolong survival time in mice inoculated with P388 leukemia cells (mean survival = 14.6 ± 2.4 days at 300 mg/kg/day x 5 days i.p. vs. 9.7 ± 0.6 days in controls), giving an increase in life span at this dose of 50.5%. Within this series of 4-*N*-acyl-2-thiocytosine-arabinoside derivatives the following are also included:



Compound	R1	Formula
262764	t-Bu	C ₁₄ H ₂₁ N ₃ O ₅ S
262765	CH(Ph) ₂	C ₂₃ H ₂₃ N ₃ O ₅ S

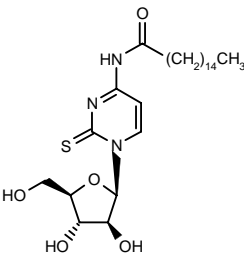
SOURCE – Toagosei.

REFERENCES

1. Saneyoshi, M. et al. (Toagosei Co., Ltd.) 4-*N*-Acyl-2-thiocytosinearabinoside and carcinostatic agents containing the same as active ingredient. JP 98036383.

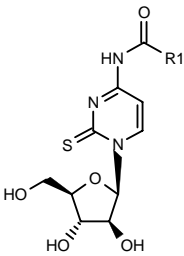
261858

1-(β-D-Arabinofuranosyl)-*N*⁴-hexadecanoyl-2-thiocytosine



C25-H43-N3-O5-S; Mol wt: 497.69

ACTION – Antineoplastic agent proven to prolong survival time in mice inoculated with P388 leukemia cells (mean survival = 16.0 ± 0.6 days at 100 mg/kg/day x 5 days i.p. vs. 9.2 ± 0.4 days in controls), giving an increase in life span of > 132.6% (5 mice survived more than 25 days) at a dose of 300 mg/kg/day x 5 days i.p. Within this series of 4-*N*-acyl-2-thiocytosine-arabinoside derivatives, the following are also included:



Compound	R1	Formula
262770	C11H23	C ₂₁ H ₂₅ N ₃ O ₅ S
262771	C13H27	C ₂₃ H ₂₉ N ₃ O ₅ S
262772	C17H35	C ₂₇ H ₄₇ N ₃ O ₅ S
262773	C21H43	C ₃₁ H ₃₅ N ₃ O ₅ S

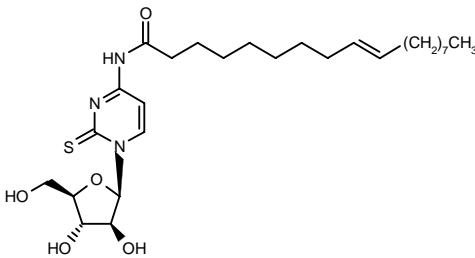
SOURCE – Toagosei.

REFERENCES

1. Saneyoshi, M. et al. (Toagosei Co., Ltd.) 4-*N*-Acyl-2-thiocytosinearabinosides and carcinostatic agents containing the same as active ingredient. JP 98036384.

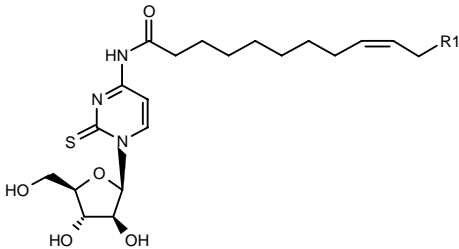
261859

1-(β-D-Arabinofuranosyl)-*N*⁴-[9(*E*)-octadecenoyl]-2-thiocytosine



C27-H45-N3-O5-S; Mol wt: 523.73

ACTION – Antineoplastic agent proven to prolong survival time in mice inoculated with P388 leukemia cells (mean survival = 17.6 ± 1.6 days at 100 mg/kg/day x 5 days i.p. vs. 9.2 ± 0.4 days in controls), giving an increase in life span at this dose of 91.3%. Within this series of 4-*N*-acyl-2-thiocytosine-arabinoside derivatives, the following are also included:



Compound	R1	Formula
262766	C7H15	C ₂₇ H ₄₅ N ₃ O ₅ S
262767	(<i>Z</i>)-CH=CHC5H11	C ₂₇ H ₄₃ N ₃ O ₅ S

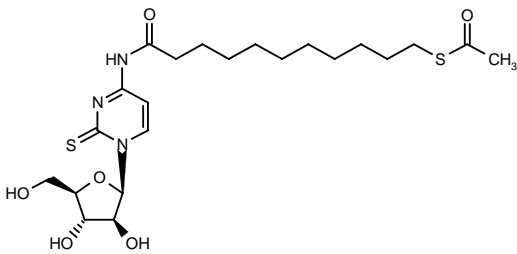
SOURCE – Toagosei.

REFERENCES

1. Saneyoshi, M. et al. (Toagosei Co., Ltd.) 4-*N*-Acyl-2-thiocytosinearabinoside and carcinostatic agents containing the same as active ingredient. JP 98036385.

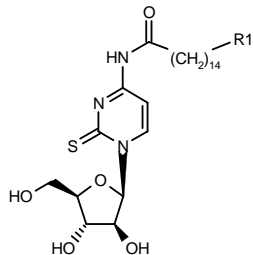
261860

1-(β-D-Arabinofuranosyl)-*N*⁴-[11-(acetylsulfanyl)-undecanoyl]-2-thiocytosine



C22-H35-N3-O6-S2; Mol wt: 501.66

ACTION – Antineoplastic agent proven to prolong survival time in mice inoculated with P388 leukemia cells (mean survival = 12.2 ± 0.4 days at 100 mg/kg/day x 5 days i.p. vs. 9.2 ± 0.4 days in controls), giving an increase in life span at this dose of 32.6%. Within this series of 4-*N*-acyl-2-thiocytosine-arabinoside derivatives, the following are also included:



Compound	R1	Formula
262768	CH2OH	C ₂₅ H ₄₃ N ₃ O ₆ S
262769	CO2H	C ₂₅ H ₄₁ N ₃ O ₇ S

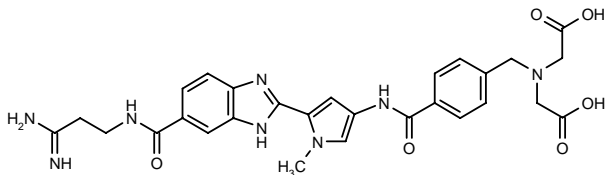
SOURCE – Toagosei.

REFERENCES

1. Saneyoshi, M. et al. (Toagosei Co., Ltd.) 4-*N*-Acyl-2-thiocytosinearabinoside and carcinostatic agents containing the same as active ingredient. JP 98036386.

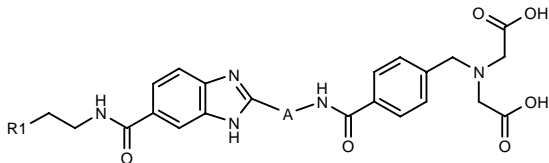
262803

N-[4-[*N*-[5-[6-[*N*-(2-Amidinoethyl)carbamoyl]-1-*H*-benzimidazol-2-yl]-1-methylpyrrol-3-yl]carbamoyl]benzyl]-iminodiacetic acid



C28-H30-N8-O6; Mol wt: 574.59

ACTION – Antineoplastic agent that acts by inducing apoptosis. A representative compound from a series of iminodiacetic acid derivatives, wherein the following are also included:



Compound	R1	A	Formula
263100	C(=NH)NH2	1-Me-pyrrol-2,5-diyl	C ₂₈ H ₃₀ N ₈ O ₆
263101	C(=NH)NH2	imidazol-2,4-diyl	C ₂₆ H ₂₇ N ₉ O ₆
263102	CH2N(Me)2	1-Me-pyrrol-2,5-diyl	C ₃₀ H ₃₅ N ₇ O ₆
263103	CH2N(Me)2	imidazol-2,4-diyl	C ₂₈ H ₃₂ N ₈ O ₆
263104	C(=NH)NH2	thien-2,4-diyl	C ₂₇ H ₂₇ N ₇ O ₆ S
263105	C(=NH)NH2	furan-2,5-diyl	C ₂₇ H ₂₇ N ₇ O ₇
263106	CH2N(Me)2	thien-2,4-diyl	C ₂₉ H ₃₂ N ₆ O ₆ S
263107	CH2N(Me)2	furan-2,5-diyl	C ₂₉ H ₃₂ N ₆ O ₇

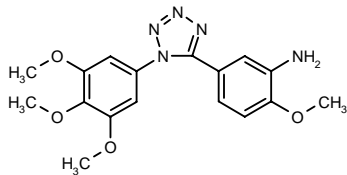
SOURCE – Mitsui Toatsu.

REFERENCES

1. Matsunaga, A. and Nakajima, Y. (Mitsui Toatsu Chem., Inc.) Iminodiacetic acid derivs. JP 98059949.

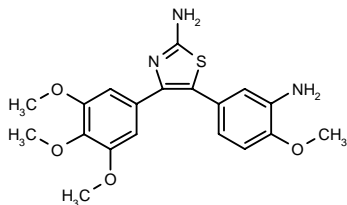
262831

2-Methoxy-5-[1-(3,4,5-trimethoxyphenyl)tetrazol-5-yl]aniline



C17-H19-N5-O4; Mol wt: 357.37

ACTION – Antineoplastic agent with potent cytotoxicity against murine colon 26 cancer cells (IC₅₀ = 2.6 ng/ml). *In vivo*, it inhibited tumor growth by 89% in mice bearing colon 26 tumors at a dose of 160 mg/kg s.c. on days 7, 11 and 15 after tumor implantation. Reported to possess low toxicity, with no deaths at up to 320 mg/kg i.v. Another related compound is:



263085: C19-H21-N3-O4-S

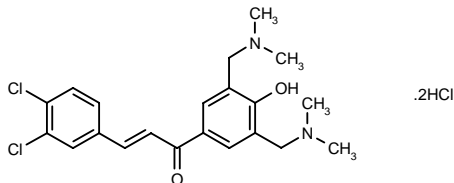
SOURCE – Ajinomoto.

REFERENCES

1. Hatanaka, T. et al. (Ajinomoto Co., Inc.) Heterocyclic derivs., and carcinostatic agents containing the same. JP 98081673.

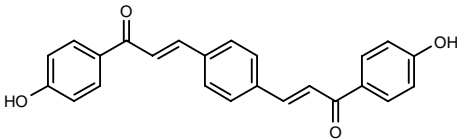
262968

(*E*)-1-[3,5-Bis(dimethylaminomethyl)-4-hydroxyphenyl]-3-(3,4-dichlorophenyl)-2-propen-1-one dihydrochloride

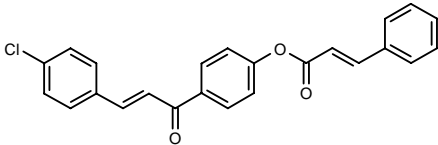


C21-H24-Cl2-N2-O2.2HCl; Mol wt: 480.26

ACTION – Antineoplastic agent with potent cytotoxicity against murine leukemia P388 (IC₅₀ = 5.09 μM) and L1210 (IC₅₀ = 2.46 μM), as well as a panel of human tumor cell lines (IC₅₀ = 2.35 μM). Other related Mannich bases of chalcones include the following:



262969: C24-H18-O4



262970: C24-H17-Cl-O3

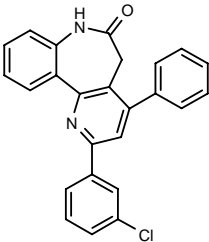
SOURCES – Univ. Alberta, Edmonton, Alberta (CA); Natl. Cancer Inst., Bethesda, MD (US); Rega Inst. Med. Res., Katholieke Univ. Leuven, Leuven (BE); Univ. Saskatchewan, Saskatoon, Saskatchewan (CA); Wayne State Univ., Detroit, MI (US); Univ. Windsor, Windsor, Ontario (CA).

REFERENCES

1. Dimmock, J.R. et al. *Cytotoxic activities of Mannich bases of chalcones and related compounds.* J Med Chem 1998, 41(7): 1014.

263130

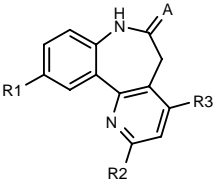
2-(3-Chlorophenyl)-4-phenyl-6,7-dihydro-5H-pyrido-[3,2-d][1]benzazepin-6-one



C25-H17-Cl-N2-O; Mol wt: 396.88

Colorless crystals, m.p. 287 °C.

ACTION – Antineoplastic agent proven to selectively inhibit the growth of renal cancer cell lines such as 786-O, ACHN and TK-10 (log GI₅₀ = –6.01, –5.94 and –5.83 M, respectively), inducing cell death (log LC₅₀ = –5.27, –4.61 and –4.76 M, respectively). Selected for further studies along with the following lactams or thiolactams:



Compound	R1	R2	R3	A	Formula
263131	H	Ph	4-Br-Ph	O	C ₂₅ H ₁₇ BrN ₂ O
263132	Br	Ph	Ph	O	C ₂₅ H ₁₇ BrN ₂ O
263133	H	3-Cl-Ph	Ph	S	C ₂₅ H ₁₇ ClN ₂ S
263134	H	Ph	4-Br-Ph	S	C ₂₅ H ₁₇ BrN ₂ S
263135	Br	Ph	Ph	S	C ₂₅ H ₁₇ BrN ₂ S

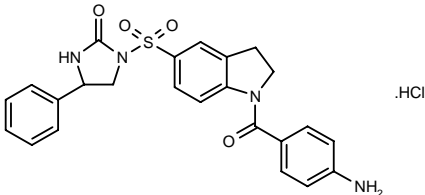
SOURCE – Univ. Hamburg, Hamburg (DE).

REFERENCES

1. Link, A. and Kunick, C. *d-Fused[1]benzazepines with selective in vitro antitumor activity: Synthesis and structure-activity relationships.* J Med Chem 1998, 41(8): 1299.

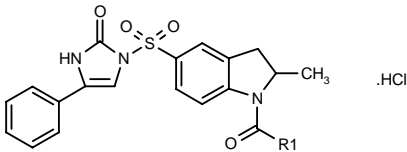
263304

1-[1-(4-Aminobenzoyl)indolin-5-ylsulfonyl]-4-phenyl-imidazolidin-2-one hydrochloride

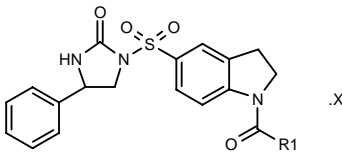


C24-H22-N4-O4-S.HCl; Mol wt: 498.98

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against human lung carcinoma A549, human chronic myelogenous leukemia K562 and human ovarian adenocarcinoma SK-OV-3 cells (IC₅₀ = 0.090, 0.203 and 0.572 µg/ml, respectively). *In vivo*, it prolonged median survival time in mice bearing murine leukemia P388 (T/C x 100 = 166.7 and 175.0% at 100 mg/kg/day i.p. or p.o., respectively) and produced 67.4% inhibition of the growth of murine colon 26 tumors implanted intradermally in nude mice at 65 mg/kg/day p.o. A representative compound from a series of arylsulfonylimidazoline derivatives, wherein the following are also included:



Compound	R1	Formula
263986	4-NH2-Ph	C ₂₅ H ₂₃ ClN ₄ O ₄ S
263987	t-BuNHCH2	C ₂₄ H ₂₉ ClN ₄ O ₄ S

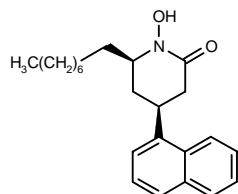


Compound	R1	Isomer	X	Formula
263988	NHEt			C ₂₀ H ₂₂ N ₄ O ₄ S
263989	NHPh			C ₂₄ H ₂₂ N ₄ O ₄ S
263990	4-Me-Ph			C ₂₅ H ₂₃ N ₃ O ₄ S
263991	4-NH2-Ph	(+)-(S)	HCl	C ₂₄ H ₂₂ N ₄ O ₄ S.HCl
263992	4-[PhCH2CH(NH2)-CONH]-Ph	(-)-(S)	HCl	C ₃₃ H ₃₁ N ₅ O ₅ S.HCl

SOURCE – Dong Wha.

REFERENCES

1. Yoon, S.J. et al. (Dong Wha Pharm. Ind., Co., Ltd.) *Arylsulfonylimidazolone derivs. as an antitumor agent.* WO 9807719.

BMD-188***200397***cis*-1-Hydroxy-4-(1-naphthyl)-6-octylpiperidin-2-one

C23-H31-N-O2; Mol wt: 353.50

ACTION – Antineoplastic agent proven to block the growth of androgen-independent prostate cancer PC3 cells (LD₅₀ approx. 10 μM) via the induction of apoptosis. Compound also caused apoptosis, regardless of androgen dependence and p53 status, in other types of prostate cancer cells, including cells with the multidrug resistance phenotype. Moreover, BMD-188 demonstrated 2-5-fold lower cytotoxicity towards several normal cell types examined. Administered peritoneally, it significantly inhibited the growth and local invasion of prostate Du145 tumors implanted into SCID mice.

SOURCES – Vanderbilt Univ., Nashville, TN (US); Wayne State Univ., Detroit, MI (US).

REFERENCES

1. Honn, K.V. et al. (Wayne State Univ.; Vanderbilt Univ.) *Cyclic hydroxamic acids*. US 5234933, WO 9308803.

2. Tang, D.G. et al. A novel hydroxamic acid compound, BMD188, demonstrates potent anti-prostate cancer effect in vitro and in vivo by inducing apoptosis in a p53-independent manner. *Proc Amer Soc Clin Oncol* 1998, 17: Abst 1330.

*Identified compound **200397** (see **197399**) Drug Data Rep 1993, 15(10): 913.

DAB₃₈₉IL-7**261655**

Recombinant fusion protein composed of the catalytic and transmembrane domains of diphtheria toxin fused to IL-7

ACTION – A recombinant IL-7 receptor-targeted fusion toxin composed of the catalytic and transmembrane domains of diphtheria toxin genetically fused to IL-7. Compound exerted selective cytotoxic activity in the IL-7 receptor-positive pre-B cell line 2E8 (IC₅₀ = 0.1 nM), but not the IL-7 receptor-negative human T-leukemia cell line HUT 102/6TG. It was shown to bind to the IL-7 receptor on 2E8 cells, resulting in signal transduction and stimulation of cell proliferation.

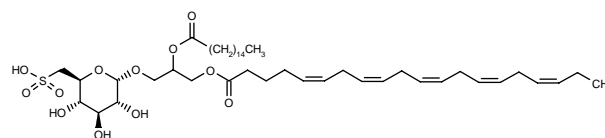
SOURCE – Boston Med. Center, Boston, MA (US).

REFERENCES

1. Sweeney, E.B. et al. *Interleukin 7 (IL-7) receptor-specific cell killing by DAB389 IL-7: A novel agent for the elimination of IL-7 receptor positive cells*. *Bioconjugate Chem* 1998, 9(2): 201.

KM-043**263177**

(*all Z*)-5,8,11,14,17-Icosapentaenoic acid 3-(6-deoxy-6-sulfo-α-D-glucopyranosyloxy)-2-(hexadecanoyloxy)propyl ester



C45-H76-O12-S; Mol wt: 841.15

Colorless amorphous powder, [α]_D +57.02° (c 0.11, MeOH).

ACTION – Sulfolipid isolated from the marine red alga *Gigartina tenella*, a potent inhibitor of eukaryotic DNA polymerases α and β (IC₅₀ = 0.25 and 3.6 μM, respectively) and HIV-1 reverse transcriptase (IC₅₀ = 11.2 μM). Compound also showed cytotoxicity to HeLa S3 cells at low concentrations.

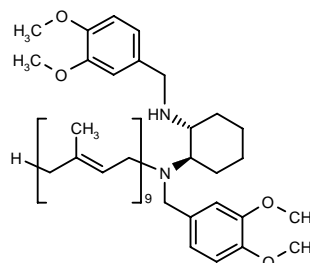
SOURCE – Toyo Suisan.

REFERENCES

1. Ohta, K. et al. *Sulfoquinovosyldiacylglycerol, KM043, a new potent inhibitor of eukaryotic DNA polymerases and HIV-reverse transcriptase type 1 from a marine red alga, Gigartina tenella*. *Chem Pharm Bull* 1998, 46(4): 684.

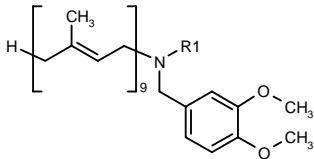
RESISTANCE MODIFIERS**257479**

trans-(*all E*)-*N,N'*-Bis(3,4-dimethoxybenzyl)-*N*-(3,7,11,15,19,23,27,31,35-nonamethyl-2,6,10,14,18,22,26,30,34-hexatriacontanonaenyl)cyclohexane-1,2-diamine



C69-H106-N2-O4; Mol wt: 1027.61

ACTION – Antineoplastic enhancer and multidrug resistance-reversing agent shown to potentiate the carcinostatic activity of doxorubicin against human breast cancer MCF-7 cells (IC₅₀ doxorubicin = 10 ng/ml in the absence of test compound vs. 5.2 ng/ml when combined with 50 μM of test compound), and to reverse resistance to doxorubicin in MCF-7/ADM cells, the IC₅₀ value being 1250 ng/ml in the absence of test compound and 30 ng/ml when doxorubicin was combined with 50 μM of test compound. Other compounds from this series of isoprene derivatives include the following:



Compound	R1	Formula
262994	1-[3,4-(MeO)2-PhCH2]-3-pyrrolidinyl	C ₆₇ H ₁₀₂ N ₂ O ₄
262995	4-[3,4-(MeO)2-PhCH2-NH(CH2)3]-1-Piz-(CH2)3	C ₇₃ H ₁₁₆ N ₄ O ₄
262996	3-[3,4-(MeO)2-PhCH2NHCH2]-PhCH2	C ₇₁ H ₁₀₄ N ₂ O ₄

SOURCE – Nisshin Flour Milling.

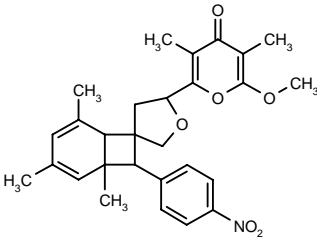
REFERENCES

1. Inomata, K. et al. (Nisshin Flour Milling Co., Ltd.) *Isoprene derivs.* EP 787716, JP 97268162.

SNF-4435C

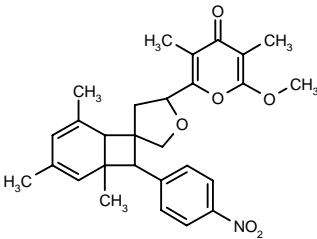
262541

(-)-2-Methoxy-3,5-dimethyl-6-[1,3,5-trimethyl-8-(4-nitrophenyl)spiro[bicyclo[4.2.0]octa-1,3,5-triene-7,3'-tetrahydrofuran]-5'-yl]-4*H*-pyran-4-one



C28-H31-N-O6; Mol wt: 477.56

ACTION – Immunosuppressant with multidrug resistance (MDR)-reversing activity, isolated from cultures of *Streptomyces spectabilis* SNF4435. Another compound from this source is:



SNF-4435D [262542]: C28-H31-N-O6: (+)-isomer

SOURCE – Snow Brand Milk Products.

REFERENCES

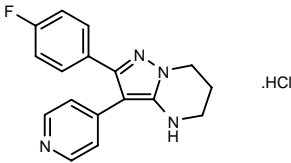
1. Kurosawa, K. et al. (Snow Brand Milk Prods. Co., Ltd.) *Novel physiologically active substance and process for producing the same.* WO 9743434.
2. Kurosawa, K. et al. *Multidrug resistance-reversing effect of novel immunosuppressor, SNF4435C.* Nippon Nogeikagaku Kaishi 1998, 72(3, Suppl.): Abst 3A10a6.

CHEMOPROTECTIVE AGENTS

FR-143430*

194942

2-(4-Fluorophenyl)-3-(4-pyridyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrimidine hydrochloride



C17-H15-F-N4.HCl; Mol wt: 330.79

ACTION – A dual inhibitor of IL-1 and tumor necrosis factor- α (TNF- α) production proven to inhibit the production of TNF- α , IL-1 α and IL-1 β in human leukocytes with IC₅₀ values of 0.29, 032 and 0.17 μ M, respectively, but to be inactive against IL-2, IL-6 and interferon gamma at concentrations up to 10 μ M. In a model of colon 26 adenocarcinoma-induced cachexia in BALB/c mice, when injected directly into the tumor (1 mg/tumor/day for 8 days) compound did not affect tumor growth, but it attenuated the tumor-induced reductions in body weight gain, food intake, epididymal fat and carcass weight. Treatment slowed the decrease in circulating levels of triglycerides and glucose, and the increase in circulating levels of cholesterol, free fatty acids and total protein. However, treatment with 100 mg/kg/day p.o. for 8 days was not effective in this model.

SOURCE – Fujisawa.

REFERENCES

1. Oku, T. et al. (Fujisawa Pharm. Co., Ltd.) *Condensed pyrazole derivs. with interleukin-1 and tumour necrosis factor inhibitory activity.* EP 531901, JP 94287188, JP 95252256, US 5356897, US 5478827, US 5624931.
2. Yamamoto, N. et al. *Effect of FR143430, a novel cytokine suppressive agent, on adenocarcinoma colon26-induced cachexia in mice.* Anticancer Res 1998, 18(1A): 139.

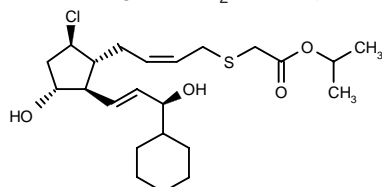
*Identified compound **194942** Drug Data Rep 1993, 15(8): 700.

OCULAR MEDICATIONS

ANTIGLAUCOMA AGENTS

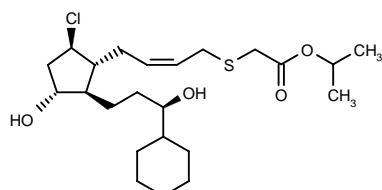
258411

9 β -Chloro-15-cyclohexyl-9-deoxy-16,17,18,19,20-pentano-3-thiaprostaglandin F₂ isopropyl ester



C23-H37-Cl-O4-S; Mol wt: 445.06

ACTION – Prostaglandin derivative with intraocular pressure-lowering activity in rabbits. Another related compound is:



263013: C23-H39-Cl-O4-S

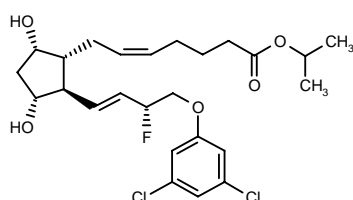
SOURCE – Taisho.

REFERENCES

1. Sato, F. et al. (Taisho Pharm. Co., Ltd.) *Prostaglandin derivs.* JP 97286775.

263882

16-(3,5-Dichlorophenoxy)-15-deoxy-15-fluoro-17,18,19,20-tetranorprostaglandin F_{2α} isopropyl ester



C25-H33-Cl2-F-O5; Mol wt: 503.44

ACTION – Antiglaucoma agent with low potential for inducing ocular irritation as compared to the reference compound latanoprost. A representative compound within a series of fluorinated prostaglandins.

SOURCES – Asahi Glass; Santen.

REFERENCES

1. Shirasawa, E. et al. (Asahi Glass Co., Ltd.; Santen Pharm. Co., Ltd.) *Fluorinated prostaglandin derivs. and medicines.* WO 9812175.

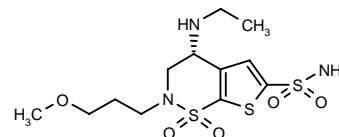
BRINZOLAMIDE⁺

Prop INN; USAN

256930

4(*R*)-(Ethylamino)-2-(3-methoxypropyl)-3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide

AL-4862



C12-H21-N3-O5-S3; Mol wt: 383.50

ACTION – Topical carbonic anhydrase inhibitor.

INDICATION – Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

PRESENTATION – Ophthalmic suspension, 1%, supplied in DROP-TAINERS(R) dispensers (2.5, 5, 10 and 15 ml).

PROPRIETARY NAME – Azopt (US).

SOURCE – Alcon.

RECENT REFERENCES

1. Camras, C.B. et al. *A triple-masked, primary therapy study of the efficacy and safety of BID and TID-dosed brinzolamide 1% compared to TID-dosed dorzolamide 2% and BID-dosed timolol 0.5%.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2606.
 2. Dean, T. et al. *Brinzolamide (AL-4862) suspension is a new topically active carbonic anhydrase inhibitor in the Dutch-belted rabbit and cynomolgus monkey.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3786.
 3. Shin, D.H. et al. *A triple-masked, placebo-controlled, adjunctive therapy study of the efficacy and safety of TID-dosed brinzolamide 1.0% compared to TID-dosed placebo when used adjunctively to timolol 0.5%.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2605.
 4. Stams, T. et al. *Structures of murine carbonic anhydrase IV and human carbonic anhydrase II complexed with brinzolamide: Molecular basis of isozyme-drug discrimination.* Protein Sci 1998, 7(3): 556.
 5. Stewart, R. et al. *The ocular comfort of TID-dosed brinzolamide 1.0% compared to TID-dosed dorzolamide 2.0% in patients with primary open-angle glaucoma or ocular hypertension.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2603.
 6. *Alcon to launch Azopt following FDA approval.* Alcon Laboratories, Inc. Press Release 1998, April 16.
 7. *Brinzolamide development status.* Alcon Laboratories, Inc. Company Communication 1998, February 16.
 8. *Brinzolamide launch.* Alcon Laboratories, Inc. Company Communication 1998, May 4.
 9. *First market introduction for Alcon's newest ophthalmic drug.* Prous Science Daily Essentials May 5, 1998.
 10. *New antiglaucoma agent approved in U.S.* Prous Science Daily Essentials April 24, 1998.
 11. *Spotlight on carbonic anhydrase inhibitors for glaucoma.* Prous Science Daily Essentials November 25, 1997.
- MONOGRAPH** – Wroblewski, T. et al. *Brinzolamide.* Drugs Fut 1998, 23(4): 365.

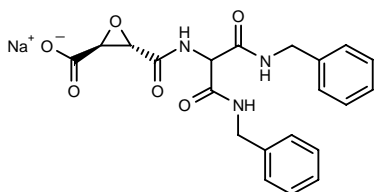
⁺Drug Data Rep 1997, 19(11): 1044.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

261854

N-[Bis(*N*-benzylcarbamoyl)methyl]-2(*S*),3(*S*)-epoxysuccinamic acid sodium salt



C21-H20-N3-Na-O6; Mol wt: 433.40

ACTION – A potent inhibitor of cathepsin B and cathepsin L (IC_{50} = 0.13 μ M and 1.2 nM, respectively). Potentially useful for the treatment of osteoporosis, neoplastic diseases, periodontitis and rheumatoid arthritis.

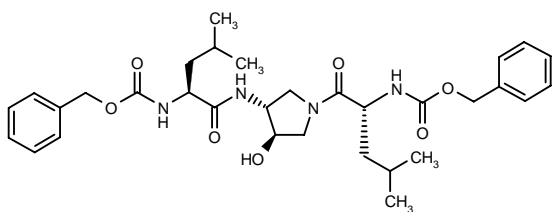
SOURCE – Nippon Chemiphar.

REFERENCES

1. Nomura, Y. and Takahashi, T. (Nippon Chemiphar Co., Ltd.) *Malonic acid derivs.* JP 98036363.

262910

trans-*N* ^{α} -(Benzyloxycarbonyl)-*N*¹-[1-[*N*-(benzyloxycarbonyl)-L-leucyl]-4-hydroxypyrrolidin-3-yl]-L-leucinamide



C32-H44-N4-O7; Mol wt: 596.72

ACTION – Agent for the treatment of disorders characterized by excessive bone or cartilage loss such as osteoporosis, periodontitis and arthritis that acts by inhibiting cysteine proteases, particularly cathepsin K.

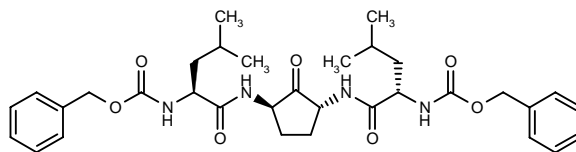
SOURCE – SmithKline Beecham.

REFERENCES

1. Marquis, R.W. Jr. et al. (SmithKline Beecham Corp.) *Inhibitors of cysteine protease.* WO 9805336.

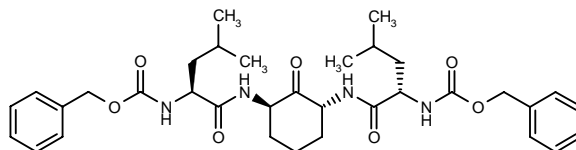
263336

trans-1,3-Bis(benzyloxycarbonyl-L-leucylamino)-cyclopentanone



C33-H44-N4-O7; Mol wt: 608.73

ACTION – Agent for the treatment of osteoporosis and other diseases characterized by bone loss, an inhibitor of cysteine proteases, particularly cathepsin K. Another specifically claimed compound is:



264139: C34-H46-N4-O7

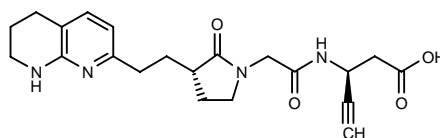
SOURCE – SmithKline Beecham.

REFERENCES

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263358

3(*S*)-[2-[2-Oxo-3(*S*)-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl]acetamido]-4-pentynoic acid



C21-H26-N4-O4; Mol wt: 398.46

ACTION – Nonpeptide integrin, particularly $\alpha v \beta 3$ (vitronectin receptor), antagonist useful for inhibiting bone resorption and with potential in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation.

SOURCE – Merck & Co.

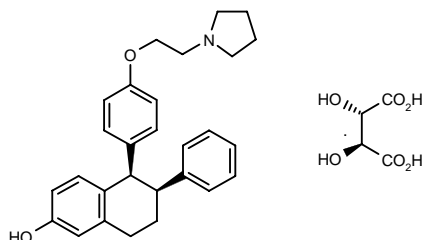
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CP-336156

236902

(-)-(5*R*,6*S*)-6-Phenyl-5-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol (-)-D-tartrate salt



C28-H31-N-O2.C4-H6-O6; Mol wt: 563.65

ACTION – Nonsteroidal estrogen receptor partial agonist that binds selectively and with high affinity to the human estrogen receptor ER α (IC₅₀ = 1.5 nM) and exerts estrogen-like effects in preventing bone loss and lowering serum cholesterol levels but does not stimulate the uterus. In ovariectomized rats, it was much more potent than raloxifene and droloxifene in preventing bone loss and at least as effective as estradiol. Its mechanism of action in bone appears to involve the induction of p53-mediated apoptosis. Currently in clinical trials for the treatment or prevention of postmenopausal osteoporosis.

SOURCES – Ligand; Pfizer.

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7. Ke, H.Z. et al. *Effects of CP-336,156, a new nonsteroidal estrogen agonist/antagonist, on bone, serum cholesterol, uterus and body composition in rat models*. Endocrinology 1998, 139(4): 2068.
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LEVORMELOXIFENE

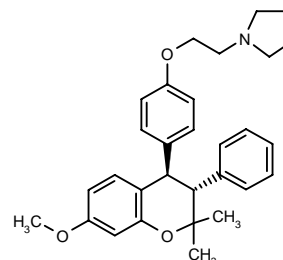
Prop INN

224036

(-)-(3*R*,4*R-trans*)-7-Methoxy-2,2-dimethyl-3-phenyl-4-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]chromane

(-)-(3*R*,4*R-trans*)-1-[2-[4-(7-Methoxy-2,2-dimethyl-3-phenyl-4-chromanyl)phenoxy]ethyl]pyrrolidine

NNC-46-0020



C30-H35-N-O3; Mol wt: 457.61

ACTION – Nonsteroidal estrogen receptor partial agonist, the most potent enantiomer of ormeloxifene (Centchroman), that acts like estrogen on bone without stimulating the uterus and breast. Currently undergoing phase III trials for the treatment and prevention of postmenopausal osteoporosis. It has also demonstrated antiatherogenic and hypocholesterolemic effects.

SOURCES – Novo Nordisk; Takeda.

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13. Bain, S. et al. *Levormeloxifene, a non-steroidal estrogen receptor therapeutic, prevents bone loss, reduces serum cholesterol, and has differentiated uterine, effects in the ovariectomized rat.* Maturitas 1997, 27(Suppl.): 144.

14. Bjarnason, K. et al. *Levormeloxifene, a new partial estrogen receptor agonist demonstrates antiresorptive and antiatherogenic properties in postmenopausal women.* J Bone Miner Res 1997, 12(Suppl. 1): Abst F479.

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30. *Proposed international nonproprietary names: List No. 73.* WHO Drug Inform 1995, 9(2): 91.

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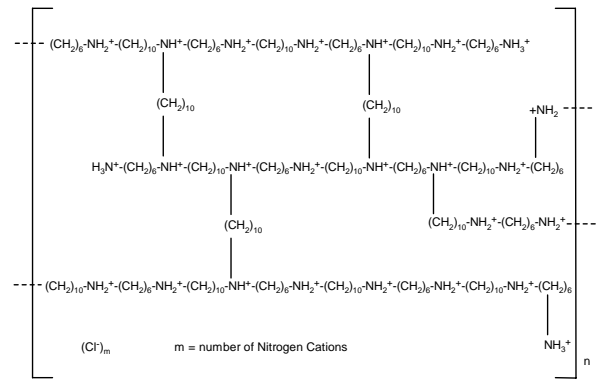
TREATMENT OF LIPOPROTEIN DISORDERS

DMP-504

224679

Crosslinked polymer of 1,6-hexanediamine with 1,10-dibromodecane

1,6-Diaminohexane-1,10-dibromodecane copolymer



(C18-H40-N2-Cl2)n

ACTION – Potent hydrogel bile acid sequestrant for the treatment of hypercholesterolemia. Studies in hamsters have shown that title compound (20-1000 mg/kg/day x 14 days in the feed) increases fecal bile acids, fecal sterols and hepatic cholesterol 7α-hydroxylase activity and decreases total serum cholesterol, non-HDL cholesterol and HDL cholesterol, being more potent than cholestyramine (50-1000 mg/kg/day x 14 days in the feed). Clinical studies in hypercholesterolemic subjects showed that oral DMP-504 (0.9-7.2 g/day x 14 days or 0.9-5.4 g/day x 42 days) significantly decreased serum LDL cholesterol levels with an acceptable side effect profile.

SOURCE – DuPont Merck.

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7. Hainer, J.W. et al. *DMP 504, a novel hydrogel bile acid sequestrant: III. Safety, tolerability, and cholesterol-lowering in healthy hypercholesterolemic subjects.* Drug Develop Res 1997, 41(2): 76.

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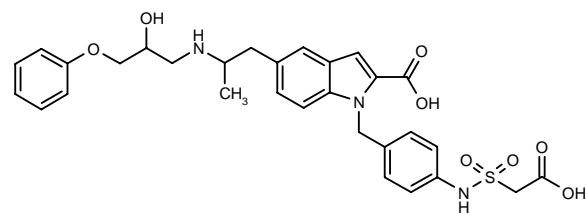
12. *DuPont Merck will outlicense bile acid sequestrant compound; cholesterol-lowering agent prepared to start phase 3 testing.* DuPont Merck Press Release 1997, June 23.

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ANTI OBESITY DRUGS

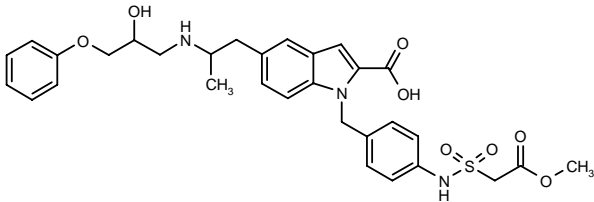
262078

1-[4-(Carboxymethylsulfonamido)benzyl]-5-[2-(2-hydroxy-3-phenoxypropylamino)propyl]-1*H*-indole-2-carboxylic acid



C30-H33-N3-O8-S; Mol wt: 595.67

ACTION – Agent for the treatment of obesity and diabetes with selective β_3 -adrenoceptor-agonist activity. Also claimed for use in the treatment of intestinal motility disorders, depression, prostate disorders, dyslipidemia and airways inflammatory disorders. Another specifically claimed compound from this series of indole-2-carboxylic acid derivatives is:



263379: C31-H35-N3-O8-S

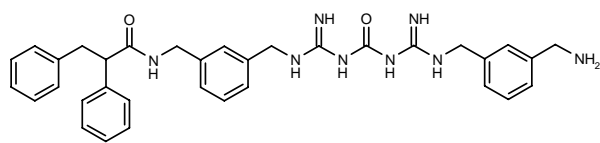
SOURCE – Pfizer.

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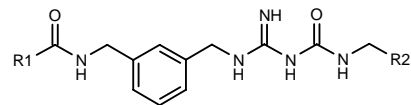
263273

N-[*N*-[3-(Aminomethyl)benzyl]amidino]-*N*'-[*N*-[3-(2,3-diphenylpropionamidomethyl)benzyl]amidino]urea



C34-H38-N8-O2; Mol wt: 590.73

ACTION – Agent that binds with high affinity to neuropeptide Y (NPY) receptors, as demonstrated in binding studies by an IC₅₀ value of 70 nM against [¹²⁵I]-PYY binding to NPY receptors in membranes derived from the human neuroblastoma cell line SK-N-MC. Potentially useful in the treatment of obesity, anxiety, hypertension and other pathological conditions. Other specifically claimed compounds from this series of amidino-urea or diamidino-urea derivatives acting as agonists, partial agonists, antagonists or mixed agonist–antagonists of NPY include the following:



Compound	R1	R2	Formula
263906	CH(Ph)CH2Ph	3-[NH2C(=NH)-NHCH2]-Ph	C ₃₄ H ₃₈ N ₈ O ₂
263907	NHCH(Ph)CH2Ph	3-(NH2CH2)-Ph	C ₃₃ H ₃₇ N ₇ O ₂
263908	CH(Ph)CH2Ph	3-Pyr	C ₃₁ H ₃₂ N ₆ O ₂

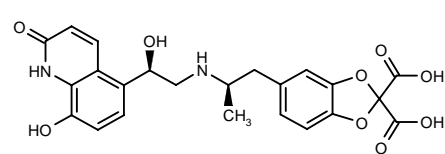
SOURCE – Agouron.

REFERENCES

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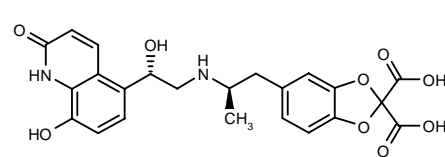
263493

5-[2(*R*)-[2(*R*)-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]propyl]-1,3-benzodioxole-2,2-dicarboxylic acid



C23-H22-N2-O9; Mol wt: 470.43

ACTION – Agent for the treatment of obesity and diabetes with selective β_3 -adrenoceptor-agonist activity. Another specifically claimed compound is:



263747: C23-H22-N2-O9

SOURCE – SmithKline Beecham.

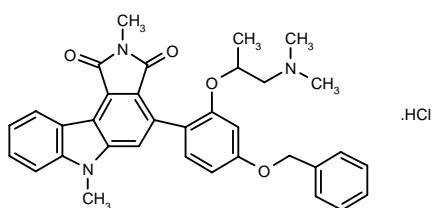
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1. Beeley, L.J. and Dean, D.K. (SmithKline Beecham plc) *Heterocyclic ethanolamine derivs. with β -adrenoreceptor agonistic activity*. US 5750701, WO 9525104.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

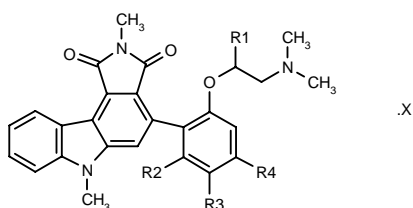
263805

4-[4-Benzyloxy-2-[2-(dimethylamino)-1-methylethoxy]-phenyl]-2,6-dimethyl-1,2,3,6-tetrahydropyrrolo[3,4-c]-carbazole-1,3-dione hydrochloride



C34-H33-N3-O4.HCl; Mol wt: 584.11

ACTION – Agent for the treatment of thrombopenia that acts by promoting thrombopoiesis, as demonstrated by its ability to increase platelet count by 384% in irradiated mice at a dose of 10 mg/kg/day s.c. x 5 days. Within this series of pyrrolocarbazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
264986	H	H	H	CH2OH		C ₂₇ H ₂₇ N ₃ O ₄
264987	Me	Br	H	H	HCl	C ₂₇ H ₂₆ BrN ₃ O ₃ .HCl
264988	Me	H	Br	H	HCl	C ₂₇ H ₂₆ BrN ₃ O ₃ .HCl

SOURCE – Kyowa Hakko.

REFERENCES

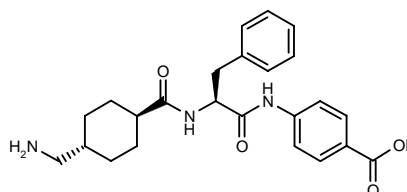
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PHARMACOLOGICAL TOOLS

262026

trans-N²-[4-(Aminomethyl)cyclohexylcarbonyl]-N¹-(4-carboxyphenyl)-L-phenylalaninamide

trans-4-[2(*S*)-[4-(Aminomethyl)cyclohexylcarboxamido]-3-phenylpropionamido]benzoic acid



C24-H29-N3-O4; Mol wt: 423.51

Amorphous powder, $[\alpha]_D^{25} +32.1^\circ$ (c 0.62, AcOH).

ACTION – Potent and highly selective plasma kallikrein (PK) inhibitor, as demonstrated in an amidolytic assay (IC₅₀ = 2.7 μ M), with less activity against plasmin (IC₅₀ = 1400 μ M) or trypsin (IC₅₀ = 26 μ M), giving selectivity ratios of 519 and 9.6 for plasmin/PK and trypsin/PK, respectively.

Inhibitors of PK may be useful in the treatment of asthma, allergic rhinitis and arthritis, and as tools for studying the physiological role of the enzyme.

SOURCE – Showa Denko.

REFERENCES

1. Katsuura, Y. et al. (Showa Denko K.K.) *Agent for treating pancreatitis or the like*. EP 369035, JP 90506190, WO 8911852.

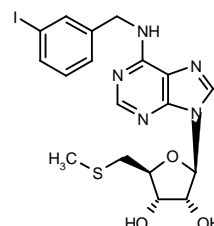
2. Oguro, K. et al. (Showa Denko K.K.) *Anti-ulcer compsn*. EP 317959, US 4954512.

3. Tsuda, Y. et al. *Design of plasma kallikrein inhibitors: Functional and structural requirements of plasma kallikrein inhibitors*. Chem Pharm Bull 1998,46(3): 452.

LUF-5409

263715

5'-Deoxy-N⁶-(3-iodobenzyl)-5'-(methylsulfanyl)adenosine



C18-H20-I-N5-O3-S; Mol wt: 513.35

ACTION – Adenosine analog, a high-affinity and selective ligand for the adenosine A₃ receptor (K_i = 6.9 nM in membranes from HEK 293 cells expressing human A₃ receptors); compound stimulated [³⁵S]-GTP γ S binding in membranes from CHO cells expressing human A₃ receptors, demonstrating partial agonist activity in this assay. Other compounds from this series of adenosine analogs include the following:

SOURCE – SmithKline Beecham.

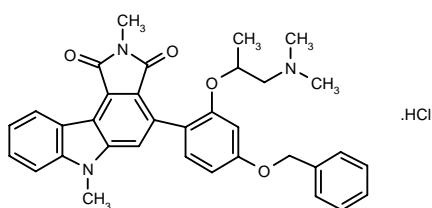
REFERENCES

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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

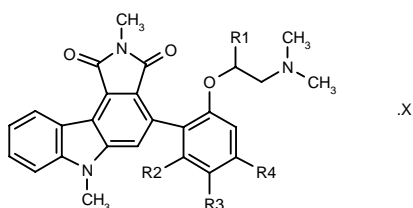
263805

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C34-H33-N3-O4.HCl; Mol wt: 584.11

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Compound	R1	R2	R3	R4	X	Formula
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264987	Me	Br	H	H	HCl	C ₂₇ H ₂₆ BrN ₃ O ₃ .HCl
264988	Me	H	Br	H	HCl	C ₂₇ H ₂₆ BrN ₃ O ₃ .HCl

SOURCE – Kyowa Hakko.

REFERENCES

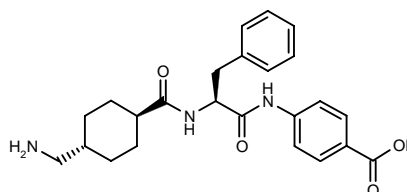
1. Ino, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Pyrrolocarbazole derivs*. WO 9809967.

PHARMACOLOGICAL TOOLS

262026

trans-*N*²-[4-(Aminomethyl)cyclohexylcarbonyl]-*N*¹-(4-carboxyphenyl)-L-phenylalaninamide

trans-4-[2(*S*)-[4-(Aminomethyl)cyclohexylcarboxamido]-3-phenylpropionamido]benzoic acid



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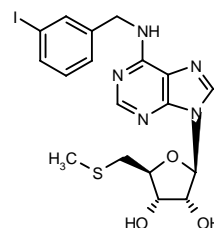
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3. Tsuda, Y. et al. *Design of plasma kallikrein inhibitors: Functional and structural requirements of plasma kallikrein inhibitors*. Chem Pharm Bull 1998,46(3): 452.

LUF-5409

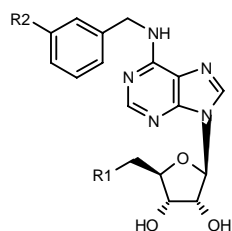
263715

5'-Deoxy-*N*⁶-(3-iodobenzyl)-5'-(methylsulfanyl)adenosine



C18-H20-I-N5-O3-S; Mol wt: 513.35

ACTION – Adenosine analog, a high-affinity and selective ligand for the adenosine A₃ receptor ($K_i = 6.9 \text{ nM}$ in membranes from HEK 293 cells expressing human A₃ receptors); compound stimulated [³⁵S]-GTP γ S binding in membranes from CHO cells expressing human A₃ receptors, demonstrating partial agonist activity in this assay. Other compounds from this series of adenosine analogs include the following:



Compound	R1	R2	Formula
LUF-5401 [263716]	OH	H	C ₁₇ H ₁₉ N ₅ O ₄
LUF-5403 [263717]	SMe	H	C ₁₈ H ₂₁ N ₅ O ₃ S
LUF-5407 [263718]	OH	I	C ₁₇ H ₁₈ I ₂ N ₅ O ₄

Activation of adenosine A₃ receptors is known to result in the release of inflammatory mediators from mast cells, hypotension, bronchoconstriction, depression of locomotor activity and protective preconditioning of the ischemic heart.

SOURCES – Univ. Heidelberg, Heidelberg (DE); Leiden/Amsterdam Cent. Drug Res., Leiden (NL).

REFERENCES

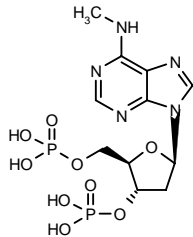
1. Van Tilburg, E.W. et al. *New partial agonists for the human adenosine A₃ receptor*. Drug Dev Res 1998, 43(1): Abst 118.

MRS-2179

263511

2'-Deoxy-*N*⁶-methyladenosine-3',5'-bisphosphate

2'-Deoxy-*N*⁶-methyl-3',5'-di-*O*-(phosphono)adenosine



C11-H17-N5-O9-P2; Mol wt: 425.23

ACTION – Potent and highly selective P2Y₁ receptor antagonist, as demonstrated by inhibition of the P2Y₁-linked phospholipase C (PLC) activation induced by the P2Y₁ full agonist 2-MeSATP in turkey erythrocyte membranes (IC₅₀ = 0.330 ± 0.059 μM; pK_B = 6.99 ± 0.13; 99 ± 1% maximum effect); it showed selectivity over other G-protein-coupled P2Y receptors expressed in human astrocytoma cells and displayed low affinity for adenosine A₁ receptors (K_i = 94.2 ± 19.8 μM for displacement of [³H]-*N*⁶-phenylisopropyladenosine binding in rat brain membranes) and no significant affinity for rat A_{2A} receptors. Title compound is the most potent antagonist reported to date for P2Y₁ receptors and has been proposed as a pharmacological tool to elucidate the physiological and pharmacological properties of the receptor in mammalian tissues.

SOURCES – Natl. Inst. Health, Bethesda, MD (US); Univ. North Carolina, Chapel Hill, NC (US).

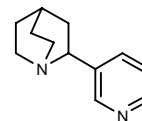
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1. Boyer, J.L. et al. *Competitive and selective antagonism of P2Y₁ receptors by N⁶-methyl 2'-deoxyadenosine 3',5'-bisphosphate*. Brit J Pharmacol 1998,124(1): 1.
2. Camaioni, E. et al. *Deoxyadenosine-bisphosphate derivatives as potent antagonists at P2Y₁ receptors*. Drug Dev Res 1998, 43(1): Abst 101.
3. Camaioni, E. et al. *Deoxyadenosine bisphosphate derivatives as potent antagonists at P2Y₁ receptors*. J Med Chem 1998, 41(2): 183.
4. Moro, S. et al. *Human P2Y₁ receptor: Molecular modeling and site-directed mutagenesis as tools to identify agonist and antagonist binding sites*. Drug Dev Res 1998, 43(1): Abst 125.
5. Moro, S. et al. *Human P2Y₁ receptor: Molecular modeling and site-directed mutagenesis as tools to identify agonist and antagonist recognition sites*. J Med Chem 1998, 41(9): 1456.

RJR-2429

259960

(±)-2-(3-Pyridyl)quinuclidine



C12-H16-N2; Mol wt: 188.27

ACTION – Potent and selective agonist at human muscle nicotinic acetylcholine receptors (nAChR; EC₅₀ = 59 nM; E_{max} = 110% vs. nicotine) with 100-1000-fold selectivity over human CNS subtypes. Compound binds with high affinity to the α4β2 receptor subtype (K_i = 1.0 nM) and chronic exposure results in significant upregulation of high-affinity [³H]-nicotine binding sites. It does not activate nicotinic receptors present in thalamic preparations, but is a potent inhibitor of this receptor subtype (IC₅₀ = 154 nM for antagonism of nicotine-stimulated ion flux in rat thalamic synaptosomes). It is also a potent partial agonist at nicotinic receptors mediating dopamine release from rat synaptosomal preparations (EC₅₀ = 2 nM; E_{max} = 40% vs. nicotine). A potentially useful ligand for elucidating the role of nAChRs in CNS function.

SOURCE – R.J. Reynolds.

REFERENCES

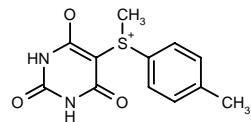
1. Bencherif, M. et al. (R.J. Reynolds Tobacco Co.) *Depolarizing skeletal muscle relaxants*. WO 9607410.
2. Bencherif, M. et al. *RJR-2429: A nicotinic agonist with selectivity for muscle nicotinic cholinergic receptors*. Soc Neurosci Abstr 1996, 22(Part 2): Abst 503.6.
3. Bencherif, M. et al. *The heterocyclic substituted pyridine derivative (±)-2-(3-pyridinyl)-1-azabicyclo[2.2.2]octane (RJR-2429): A selective ligand at nicotinic acetylcholine receptors*. J Pharmacol Exp Ther 1998, 284(3): 886.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

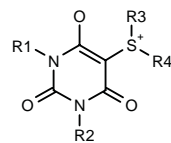
264351

5-[S-Methyl-S-(4-methylphenyl)sulfonio]-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-olate



C12-H12-N2-O3-S; Mol wt: 264.30

ACTION – Analgesic agent, a representative compound from a series of 5-sulfonio-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-olate derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
265557	H	H	Me	CH2CON(Me)Ph	C ₁₄ H ₁₅ N ₃ O ₄ S
265558	H	Et	Me	4-OH-Ph	C ₁₃ H ₁₄ N ₂ O ₄ S
265559	Me	Bu	Me	4-OH-Ph	C ₁₆ H ₂₀ N ₂ O ₄ S
265560	H	Bu	-CH2CH2OCH2CH2-		C ₁₂ H ₁₈ N ₂ O ₄ S
265561	Me	H	Me	Pr	C ₉ H ₁₄ N ₂ O ₃ S

SOURCE – Otsuka.

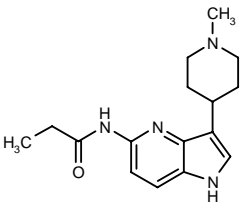
REFERENCES

1. Shibuya, T. et al. (Otsuka Pharm. Factory, Inc.) *Pyrimidine derivs.* JP 98101653.

ANTIMIGRAINE DRUGS

264669

N-[3-(1-Methylpiperidin-4-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl]propionamide



C16-H22-N4-O; Mol wt: 286.38

ACTION – Agent for the treatment of migraine and associated disorders, a selective 5-HT_{1F} agonist reported to inhibit neuronal protein extravasation due to stimulation of the trigeminal ganglia.

SOURCE – Lilly.

REFERENCES

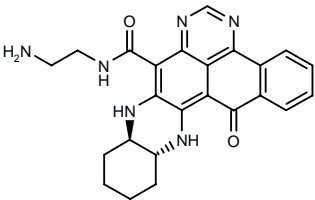
1. Filla, S.A. et al. (Eli Lilly & Co.) *5-HT_{1F} agonists.* EP 842934, WO 9820875.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

263344

(9a*R*,13a*R*)-N-(2-Aminoethyl)-15-oxo-9a,10,11,12,13,13a,14,15-octahydro-9*H*-benzo[*e*]quinoxalino[2,3-*l*]-perimidine-8-carboxamide



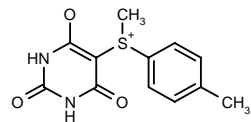
C24-H24-N6-O2; Mol wt: 428.49

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

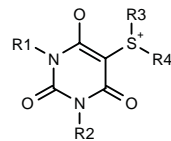
264351

5-[S-Methyl-S-(4-methylphenyl)sulfonio]-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-olate



C12-H12-N2-O3-S; Mol wt: 264.30

ACTION – Analgesic agent, a representative compound from a series of 5-sulfonio-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-olate derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
265557	H	H	Me	CH2CON(Me)Ph	C ₁₄ H ₁₅ N ₃ O ₄ S
265558	H	Et	Me	4-OH-Ph	C ₁₃ H ₁₄ N ₂ O ₄ S
265559	Me	Bu	Me	4-OH-Ph	C ₁₆ H ₂₀ N ₂ O ₄ S
265560	H	Bu	-CH2CH2OCH2CH2-		C ₁₂ H ₁₈ N ₂ O ₄ S
265561	Me	H	Me	Pr	C ₉ H ₁₄ N ₂ O ₃ S

SOURCE – Otsuka.

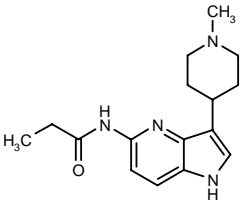
REFERENCES

1. Shibuya, T. et al. (Otsuka Pharm. Factory, Inc.) *Pyrimidine derivs.* JP 98101653.

ANTIMIGRAINE DRUGS

264669

N-[3-(1-Methylpiperidin-4-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl]propionamide



C16-H22-N4-O; Mol wt: 286.38

ACTION – Agent for the treatment of migraine and associated disorders, a selective 5-HT_{1F} agonist reported to inhibit neuronal protein extravasation due to stimulation of the trigeminal ganglia.

SOURCE – Lilly.

REFERENCES

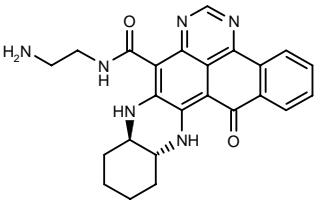
1. Filla, S.A. et al. (Eli Lilly & Co.) *5-HT_{1F} agonists.* EP 842934, WO 9820875.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

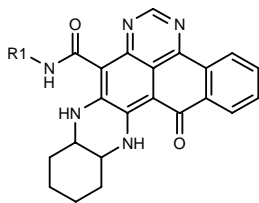
263344

(9a*R*,13a*R*)-N-(2-Aminoethyl)-15-oxo-9a,10,11,12,13,13a,14,15-octahydro-9*H*-benzo[*e*]quinoxalino[2,3-*l*]-perimidine-8-carboxamide



C24-H24-N6-O2; Mol wt: 428.49

ACTION – Potent corticotropin-releasing factor (CRF) receptor antagonist with potential in the treatment of stress-related disorders, cardiovascular, neurological and psychiatric disorders including anxiety, depression, eating disorders, supranuclear palsy, irritable bowel syndrome, gastrointestinal disorders, immune suppression, inflammatory disorders, drug and alcohol withdrawal symptoms, Alzheimer’s disease or fertility disorders. Other specifically claimed compounds from this series of benzoperimidine-carboxylic acids derivatives include the following:



Compound	R1	Isomer	Formula
264536	CH2CH2NH2	9aR, 13aS	C ₂₄ H ₂₄ N ₆ O ₂
264538	2(R)-NH2-1(R)-cyclohexyl	9aR, 13aR	C ₂₈ H ₃₀ N ₆ O ₂
264539	2(R)-NH2-1(R)-cyclohexyl	9aR, 13aS	C ₂₈ H ₃₀ N ₆ O ₂
264540	2(R)-NH2-1(R)-cyclohexyl	9aS, 13aS	C ₂₈ H ₃₀ N ₆ O ₂
264541	2(S)-NH2-1(S)-cyclohexyl	9aR, 13aR	C ₂₈ H ₃₀ N ₆ O ₂
264542	2(S)-NH2-1(S)-cyclohexyl	9aR, 13aS	C ₂₈ H ₃₀ N ₆ O ₂
264543	2(S)-NH2-1(S)-cyclohexyl	9aS, 13aS	C ₂₈ H ₃₀ N ₆ O ₂

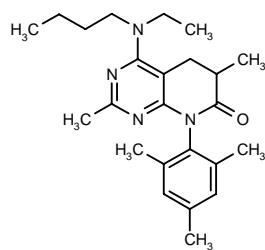
SOURCE – Agouron.

REFERENCES

1. Rabinovich, A.K. et al. (Agouron Acquisition Corp.) *Benzoperimidine-carboxylic acids and derivs. thereof.* WO 9808821.

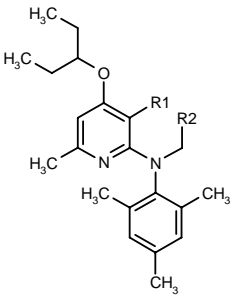
263363

4-(*N*-Butyl-*N*-ethylamino)-2,6-dimethyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-7-one

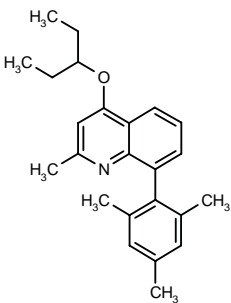


C24-H34-N4-O; Mol wt: 394.56

ACTION – Agent for the treatment of a wide variety of stress-related disorders including anxiety and depression that acts by virtue of its corticotropin-releasing factor (CRF; also known as corticotropin-releasing hormone, or CRH)-antagonist activity. Within this series of specifically claimed substituted 6,6-heterobicyclic derivatives, the following are also included:



Compound	R1,R2	Formula
265376	-NHCO-	C ₂₂ H ₂₉ N ₃ O ₂
265377	-NHCH2-	C ₂₂ H ₃₁ N ₃ O
265378	-N(Me)CO-	C ₂₃ H ₃₁ N ₃ O ₂
265380	-CH2O-	C ₂₂ H ₃₀ N ₂ O ₂
265381	-COO-	C ₂₂ H ₂₈ N ₂ O ₃



265379: C24-H29-N-O

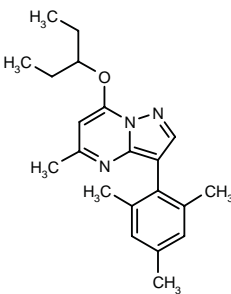
SOURCE – Pfizer.

REFERENCES

1. Chen, Y. (Pfizer, Inc.) *Substd. 6,6-hetero-bicyclic derivs.* WO 9808846.

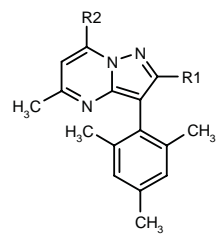
263364

7-(1-Ethylpropoxy)-5-methyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-*a*]pyrimidine

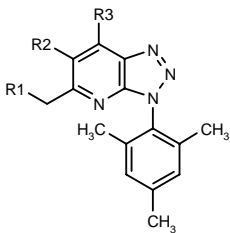


C21-H27-N3-O; Mol wt: 337.46

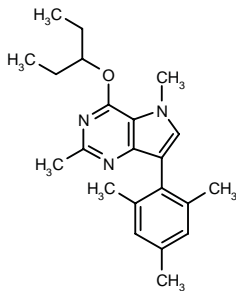
ACTION – Corticotropin-releasing factor (CRF; also known as corticotropin-releasing hormone, or CRH) antagonist with potential for the treatment of a broad range of disorders including anxiety, depression, stress-related disorders, inflammatory disorders, Alzheimer’s disease, gastrointestinal disorders, anorexia nervosa, stroke and drug and alcohol withdrawal symptoms. A representative compound from a series of substituted heterobicyclic derivatives, wherein the following are also included:



Compound	R1	R2	Formula
264698	Me	NHCH(Et)2	C ₂₂ H ₃₀ N ₄
264699	H	NHCH(Et)2	C ₂₁ H ₂₈ N ₄
264700	Me	OCH(Et)2	C ₂₂ H ₂₈ N ₃ O
264701	Me	N(Et)Pr	C ₂₂ H ₃₀ N ₄



Compound	R1	R2	R3	Formula
264702	Br	Br	NHCH(Et)2	C ₂₀ H ₂₆ Br ₂ N ₅
264703	H	H	NHCH(Et)2	C ₂₀ H ₂₇ N ₅
264704	H	Br	N(Me)CH(Et)2	C ₂₁ H ₂₈ BrN ₅
264705	H	H	OCH(Et)2	C ₂₀ H ₂₆ N ₄ O



264706: C22-H29-N3-O

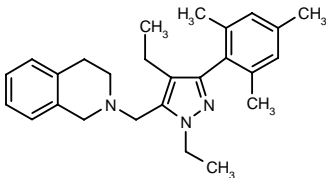
SOURCE – Pfizer.

REFERENCES

1. Chen, Y.L. (Pfizer, Inc.) *Substd. 6,5-hetero-bicyclic derivs.* WO 9808847.

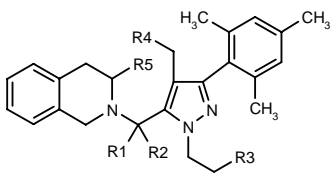
264478

2-[1,4-Diethyl-3-(2,4,6-trimethylphenyl)pyrazol-5-yl-methyl]-1,2,3,4-tetrahydroisoquinoline

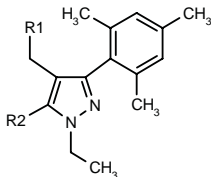


C26-H33-N3; Mol wt: 387.57

ACTION – Highly selective corticotropin-releasing factor CRF₁ receptor antagonist or partial agonist for use in the treatment of stress-related disorders such as posttraumatic stress disorder, anxiety, depression and headache. Other specifically claimed compounds within this series of pyrazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
264610	H	H	H	Me	CH2OH	C ₂₇ H ₃₅ N ₃ O
264611	H	H	H	Me	CH2OMe	C ₂₈ H ₃₇ N ₃ O
264612	H	H	H	H	H	C ₂₆ H ₃₁ N ₃
264613	H	H	H	H	CH2OH	C ₂₆ H ₃₃ N ₃ O
264614	H	H	H	H	CH2OMe	C ₂₇ H ₃₅ N ₃ O
264615	H	H	Me	H	H	C ₂₆ H ₃₃ N ₃
264616	H	H	Me	H	CH2OH	C ₂₇ H ₃₅ N ₃ O
264617	H	H	Me	H	CH2OMe	C ₂₈ H ₃₇ N ₃ O
264618	-O-		H	Me	H	C ₂₆ H ₃₁ N ₃ O



Compound	R1	R2	Formula
264619	H	2-(CH2OH)-1-Pip	C ₂₁ H ₃₁ N ₃ O
264620	Me	CON(Et)CH2Ph	C ₂₆ H ₃₃ N ₃ O
264621	Me	cyclopropyl-CH2N(Pr)CO	C ₂₄ H ₃₆ N ₃ O
264623	H	4-Me-1-Piz-CH2	C ₂₁ H ₃₂ N ₄
264624	H	4-Ph-1-Piz-CH2	C ₂₆ H ₃₄ N ₄
264625	H	4-morpholinyl-CH2	C ₂₀ H ₂₉ N ₃ O

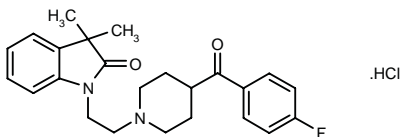
SOURCE – Neurogen.

REFERENCES

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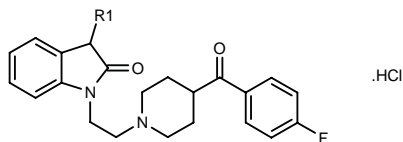
265539

1-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-3,3-dimethylindolin-2-one hydrochloride



C24-H27-F-N2-O2.HCl; Mol wt: 430.95

ACTION – Agent for the treatment of a variety of disorders including anxiety, depression, obesity, bulimia, pain, hypertension, memory loss, sexual dysfunction, schizophrenia, gastrointestinal disorders, headache, smoking cessation, drug addiction, alcoholism, emesis, Alzheimer’s disease and sleep disorders with affinity for 5-HT receptors such as 5-HT_{1D} (formerly 5-HT_{1Dα}) and 5-HT_{2A} receptors. Other compounds from this series of indol-2-one derivatives include the following:



Compound	R1	Formula
265704	Me	C ₂₃ H ₂₅ FN ₂ O ₂ .HCl
265705	i-Pr	C ₂₅ H ₂₉ FN ₂ O ₂ .HCl

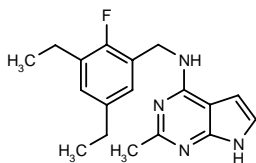
SOURCE – Lilly.

REFERENCES

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265722

N-(3,5-Diethyl-2-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine-4-amine



C18-H21-F-N4; Mol wt: 312.39

M.p. 157-9 °C.

ACTION – Anxiolytic agent whose activity was demonstrated in a conflict test in rats, with a 41% increase in punished lever pressing 1 h after oral administration of 25 mg/kg and a long duration of action (47% after 24 h). Compound appears to act through a different mechanism of action than chlordiazepoxide, showing no affinity for the benzodiazepine–GABA_A chloride channel complex or the 5-HT_{1A} receptor, but may act as a selective corticotropin-releasing factor (CRF) receptor antagonist.

SOURCE – Glaxo Wellcome.

REFERENCES

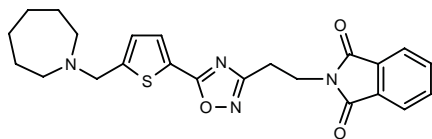
1. Meade, E.A. et al. *Anxiolytic activity of analogues of 4-benzylamino-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidines.* *Eur J Med Chem* 1998, 33(5): 363.

ANTIPSYCHOTIC DRUGS

261162

N-[2-[5-[5-(Perhydroazepin-1-ylmethyl)thiophen-2-yl]-1,2,4-oxadiazol-3-yl]ethyl]phthalimide

2-[2-[5-[2-(Perhydroazepin-1-ylmethyl)thiophen-2-yl]-1,2,4-oxadiazol-3-yl]ethyl]isoindoline-1,3-dione



C23-H24-N4-O3-S; Mol wt: 436.53

ACTION – Antipsychotic agent proven to antagonize phencyclidine (PCP) effects in rats.

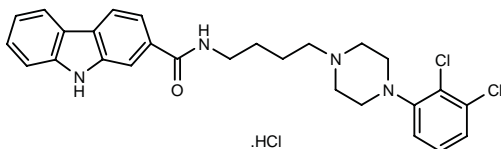
SOURCE – Yamanouchi.

REFERENCES

1. Kimura, T. et al. (Yamanouchi Pharm. Co., Ltd.) *Novel thiophene derivs. and drug compsns. containing the same.* WO 9800420.

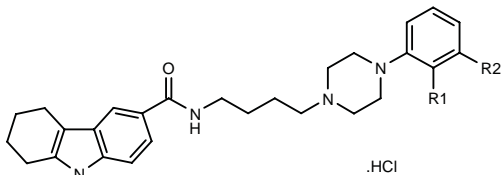
263259

N-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl]-9*H*-carbazole-2-carboxamide hydrochloride

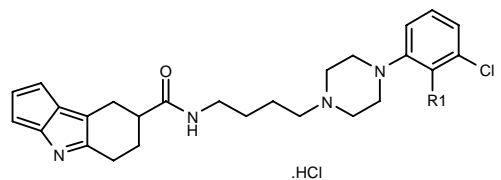


C27-H28-Cl2-N4-O.HCl; Mol wt: 531.91

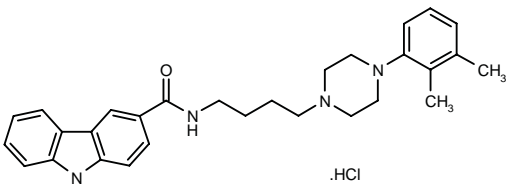
ACTION – Antipsychotic agent with high affinity and selectivity for dopamine D₃ receptors (K_i = 1 nM) relative to D₂ receptors (K_i = 750 nM). Other specifically claimed compounds from this series of fused indolecarboxamides include the following:



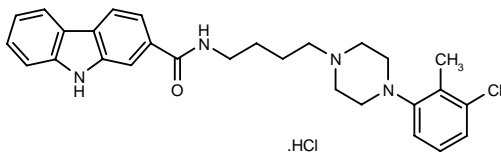
Compound	R1	R2	Formula
263690	Cl	Cl	C ₂₇ H ₃₂ Cl ₂ N ₄ O.HCl
263691	-CH=CHCH=CH-		C ₃₁ H ₃₆ N ₄ O.HCl



Compound	R1	Formula
263692	Cl	C ₂₈ H ₃₀ Cl ₂ N ₄ O.HCl
263693	Me	C ₂₇ H ₃₃ ClN ₄ O.HCl



263694: C29-H34-N4-O.HCl



263695: C28-H31-Cl-N4-O.HCl

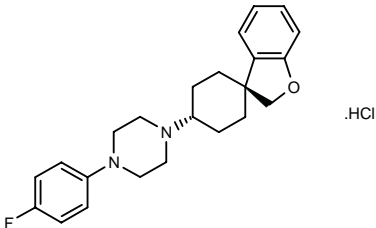
SOURCE – Neurogen.

REFERENCES

1. Yuan, J. and Wasley, J.W.F. (Neurogen Corp.) *Fused indolecarboxamides: Dopamine receptor subtype specific ligands.* WO 9806717.

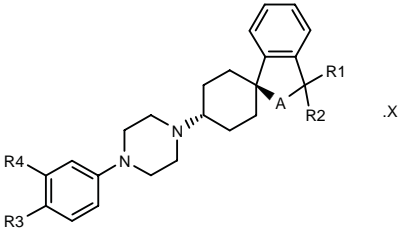
263355

trans-1-(4-Fluorophenyl)-4-(spiro[benzofuran-3(2*H*),1'-cyclohexan]-4'-yl)piperazine hydrochloride



C23-H27-F-N2-O.HCl; Mol wt: 402.94

ACTION – Antipsychotic agent with selective affinity for dopamine D₄ receptors, also claimed for the treatment or prevention of bipolar disorders, dysphoric mania, Parkinson’s disease, extrapyramidal side effects associated with neuroleptic agents, tardive dyskinesia, nausea, emesis and amenorrhea. A representative compound from a series of spirocyclic derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	A	X	Formula
264308	H	H	CN	F	O		C ₂₄ H ₂₆ FN ₃ O
264309	-O-		F	H	NH	2HCl	C ₂₃ H ₂₆ FN ₃ O.2HCl
264310	Me	Me	F	H	O	2HCl	C ₂₆ H ₃₁ FN ₂ O.2HCl

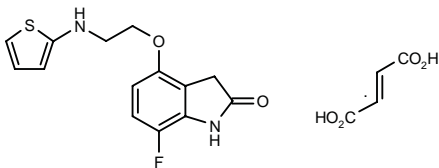
SOURCE – Pfizer.

REFERENCES

1. Butler, T.W. and Fliri, A.F.J. (Pfizer, Inc.) *Spirocyclic dopamine receptor subtype ligands.* WO 9808835.

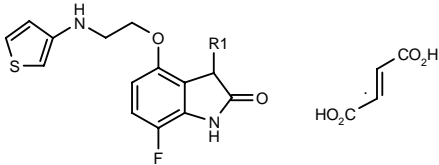
263361

7-Fluoro-4-[2-(2-thienylamino)ethoxy]indolin-2-one fumarate



C14-H13-F-N2-O2-S.C4-H4-O4; Mol wt: 408.40

ACTION – Antipsychotic agent reported to be free from extrapyramidal side effects, a selective dopamine autoreceptor agonist, as demonstrated by inhibition of [³H]-quinpirole binding in rat striatal brain preparations (IC₅₀ = 1.36 nM), with lower affinity for postsynaptic dopamine D₂ receptors (IC₅₀ = 398.4 nM against [³H]-spiroperidol binding in limbic brain preparations). Within this series of 4-aminoethoxy-indolone derivatives, the following are also specifically claimed:



Compound	R1	Formula
264446	CH2SH	C ₁₅ H ₁₅ FN ₂ O ₂ S ₂ .C ₄ H ₄ O ₄
264449	H	C ₁₄ H ₁₃ FN ₂ O ₂ S.C ₄ H ₄ O ₄

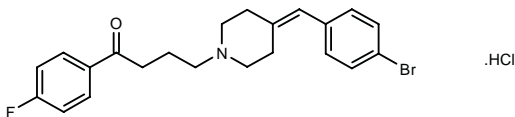
SOURCE – American Home Products.

REFERENCES

1. Mewshaw, R.E. and Webb, M.B. (American Home Prods. Corp.) *4-Aminoethoxy-indolone derivs. as dopamine D2 agonists.* WO 9808843.
2. Mewshaw, R.E. and Webb, M.B. (American Home Prods. Corp.) *4-Aminoethoxy indolone derivs.* US 5760070.

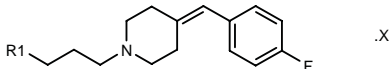
264339

4-[4-(4-Bromobenzylidene)piperidin-1-yl]-1-(4-fluorophenyl)-1-butanone hydrochloride



C22-H23-Br-F-N-O.HCl; Mol wt: 452.79

ACTION – Antipsychotic agent, a potent dopamine D₄ receptor antagonist (IC₅₀ = 5.99 nM against [³H]-spiperone binding to human receptors cloned in CHO cells) with selectivity over D₂ receptors (IC₅₀ = 97.7 nM against [³H]-raclopride binding in rat striatum membranes), expected to be free of extrapyramidal side effects. Other compounds from this series of 4-benzylidenepiperidines include the following:



Compound	R1	X	Formula
265554	4-F-PhCO		C ₂₂ H ₂₃ F ₂ NO
265555	COPh	HCl	C ₂₂ H ₂₄ FNO.HCl
265556	6-F-3-benzisoxazolyl	HCl	C ₂₂ H ₂₂ F ₂ N ₂ O.HCl

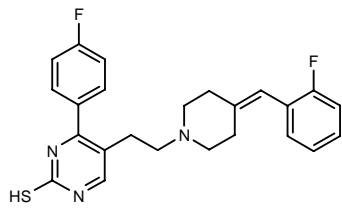
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharm. Co., Ltd.; Nihon Nohyaku Co., Ltd.) *4-Benzylidene piperidine derivs.* JP 98095770.

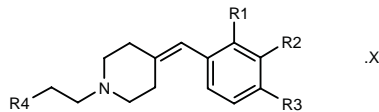
264340

5-[2-[4-(2-Fluorobenzylidene)piperidin-1-yl]ethyl]-4-(4-fluorophenyl)pyrimidine-2-thiol

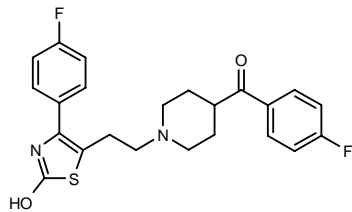


C24-H23-F2-N3-S; Mol wt: 423.52

ACTION – Antipsychotic agent, a potent dopamine D₄ receptor antagonist (IC₅₀ = 1.35 nM against [³H]-spiperone binding to human D₄ receptors cloned in CHO cells) with selectivity over D₂ receptors (IC₅₀ > 1000 nM against [³H]-raclopride binding to rat striatum membranes), expected to be free of extrapyramidal side effects. Other related compounds include the following:



Compound	R1	R2	R3	R4	X	Formula
265660	H	H	F	5-(4-F-Ph)-4-pyrazolyl		C ₂₃ H ₂₃ F ₂ N ₃
265661	H	H	Me	5-(4-F-Ph)-4-pyrazolyl	oxalate	C ₂₄ H ₂₆ FN ₃ .C ₂ H ₂ O ₄
265663	H	F	H	4-(4-F-Ph)-5-pyrimidinyl	2HCl	C ₂₄ H ₂₃ F ₂ N ₃ .2HCl
265664	F	H	H	4-(4-F-Ph)-5-pyrimidinyl	2HCl	C ₂₄ H ₂₃ F ₂ N ₃ .2HCl
265665	F	H	H	4-(4-F-Ph)-2-MeS-5-pyrimidinyl	2HCl	C ₂₅ H ₂₅ F ₂ N ₃ S .2HCl
265666	F	H	H	4-(4-F-Ph)-2-NH2-5-pyrimidinyl		C ₂₄ H ₂₄ F ₂ N ₄



265662: C23-H22-F2-N2-O2-S

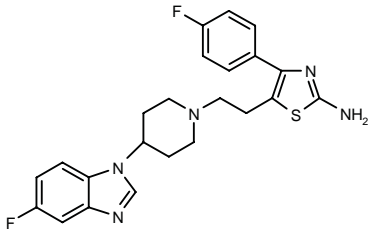
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharm. Co., Ltd.; Nihon Nohyaku Co., Ltd.) *Aromatic heterocyclic derivs.* JP 98095779.

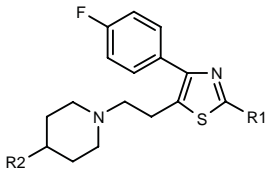
264341

5-[2-[4-(5-Fluorobenzimidazol-1-yl)piperidin-1-yl]ethyl]-4-(4-fluorophenyl)thiazol-2-amine



C23-H23-F2-N5-S; Mol wt: 439.53

ACTION – Antipsychotic agent, a potent dopamine D₄ receptor antagonist (IC₅₀ = 32.0 nM against [³H]-spiperone binding to human receptors cloned in CHO cells vs. 130.0 nM for clozapine) with selectivity over D₂ receptors (IC₅₀ > 1000 nM against [³H]-raclopride binding in rat striatum membranes vs. 394.4 nM for clozapine), expected to be free of extrapyramidal side effects. Other compounds from this series of arylpiperidines include the following:



Compound	R1	R2	Formula
265572	NH2	6-F-3-benzofuryl	C ₂₄ H ₂₃ F ₂ N ₃ OS
265573	NH2	3-indolyl	C ₂₄ H ₂₅ FN ₃ S
265574	Me	3-indolyl	C ₂₅ H ₂₆ FN ₃ S
265575	NH2	5-F-1-benzotriazolyl	C ₂₂ H ₂₂ F ₂ N ₆ S
265576	Me	5-F-1-benzotriazolyl	C ₂₃ H ₂₃ F ₂ N ₅ S

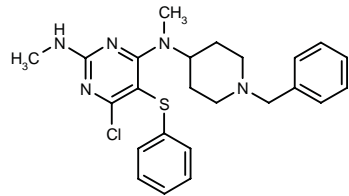
SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

1. Nagamine, M. et al. (Nihon Nohyaku Co., Ltd.; Taisho Pharm. Co., Ltd.) *Arylpiperidine derivs.* JP 98095781.

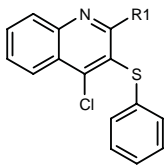
264406

N-(1-Benzylpiperidin-4-yl)-N-[6-chloro-2-(methylamino)-5-(phenylsulfanyl)pyrimidin-4-yl]-N-methylamine



C24-H28-Cl-N5-S; Mol wt: 454.03

ACTION – Antipsychotic agent, a potent and selective dopamine D₄ receptor antagonist, as demonstrated in binding assays (K_i = 1.9 and 209 nM, respectively, against [³H]-spiperone binding to human D₄ and D₂ receptors cloned in CHO cells). Other related compounds are:



Compound	R1	Formula
265441	1-(CH2Ph)-4-Pip-NH	C ₂₇ H ₂₆ ClN ₃ S
265442	4-(2-Naph-CH2)-1-Piz	C ₃₀ H ₂₆ ClN ₃ S

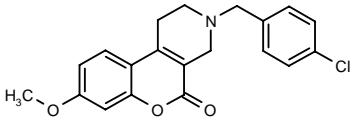
SOURCE – Sumitomo.

REFERENCES

1. Igarashi, J. et al. (Sumitomo Pharm. Co., Ltd.) *Pyrimidine derivs.* WO 9814430.

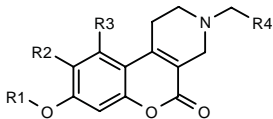
264473

3-(4-Chlorobenzyl)-8-methoxy-2,3,4,5-tetrahydro-1H-[1]benzopyrano[3,4-c]pyridin-5-one



C20-H18-Cl-N-O3; Mol wt: 355.82

ACTION – Antipsychotic agent with a low liability for extrapyramidal side effects, a selective dopamine D₄ receptor antagonist (K_i = 7.3 nM against [³H]-spiperone binding to human receptors expressed in CHO cells) with low affinity for dopamine D₂ and D₃ receptors (K_i > 5882 and 11,727 nM, respectively). Within this series of specifically claimed tetrahydrochromeno[3,4-c]pyridin-5-ones, the following are also included:



Compound	R1	R2	R3	R4	Formula
264630	H	Me	OH	Ph	C ₂₀ H ₁₉ NO ₄
264631	Me	H	H	CH2Ph	C ₂₁ H ₂₁ NO ₃
264632	Me	OMe	H	CH2Ph	C ₂₂ H ₂₃ NO ₄
264633	Me	H	H	4-quinolinyl	C ₂₃ H ₂₀ N ₂ O ₃

SOURCE – Warner-Lambert.

REFERENCES

1. Connor, D.T. et al. (Warner-Lambert Co.) *Antipsychotic method utilizing certain tetrahydrochromeno[3,4-c]pyridin-5-ones.* US 5760050.

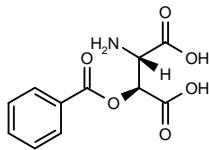
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

264675

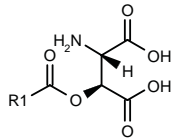
3(S)-(Benzoyloxy)-L-aspartic acid

2(S)-Amino-3(S)-(benzoyloxy)succinic acid



C11-H11-N-O6; Mol wt: 253.21

ACTION – Agent for the treatment of neuropathies and neurodegenerative diseases such as epilepsy, Huntington’s disease, amyotrophic lateral sclerosis and Alzheimer’s disease that acts by inhibiting glutamate uptake activity of L-glutamate transporters. Compound was found to inhibit glutamate uptake in *Xenopus* oocytes expressing the bovine glutamate transporter gene B6LAST (79% inhibition at 100 μM). Contrary to glutamate, compound did not induce any inward current in oocytes expressing BGLAST at 100 μM; in addition, when added simultaneously with glutamate (both at 100 μM), it reduced the inward current induced by glutamate uptake by 50%. Other compounds from this series of β-hydroxyaspartic acid derivatives include the following:

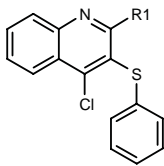


Compound	R1	Formula
265394	1-Naph	C ₁₅ H ₁₃ NO ₆
265395	2-Naph	C ₁₅ H ₁₃ NO ₆

SOURCE – Suntory.

REFERENCES

1. Shimamoto, K. et al. (Suntory, Ltd.) *β-Hydroxyaspartic acid derivs.* EP 844234.



Compound	R1	Formula
265441	1-(CH2Ph)-4-Pip-NH	C27H26ClN3S
265442	4-(2-Naph-CH2)-1-Piz	C30H26ClN3S

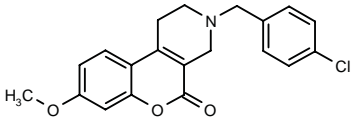
SOURCE – Sumitomo.

REFERENCES

1. Igarashi, J. et al. (Sumitomo Pharm. Co., Ltd.) *Pyrimidine derivs.* WO 9814430.

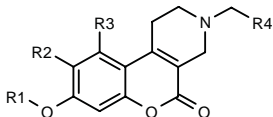
264473

3-(4-Chlorobenzyl)-8-methoxy-2,3,4,5-tetrahydro-1H-[1]benzopyrano[3,4-c]pyridin-5-one



C20-H18-Cl-N-O3; Mol wt: 355.82

ACTION – Antipsychotic agent with a low liability for extrapyramidal side effects, a selective dopamine D₄ receptor antagonist (K_i = 7.3 nM against [³H]-spiperone binding to human receptors expressed in CHO cells) with low affinity for dopamine D₂ and D₃ receptors (K_i > 5882 and 11,727 nM, respectively). Within this series of specifically claimed tetrahydrochromeno[3,4-c]pyridin-5-ones, the following are also included:



Compound	R1	R2	R3	R4	Formula
264630	H	Me	OH	Ph	C20H19NO4
264631	Me	H	H	CH2Ph	C21H21NO3
264632	Me	OMe	H	CH2Ph	C22H23NO4
264633	Me	H	H	4-quinolinyl	C23H20N2O3

SOURCE – Warner-Lambert.

REFERENCES

1. Connor, D.T. et al. (Warner-Lambert Co.) *Antipsychotic method utilizing certain tetrahydrochromeno[3,4-c]pyridin-5-ones.* US 5760050.

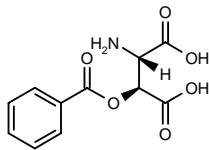
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

264675

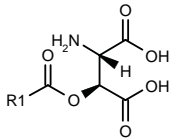
3(S)-(Benzoyloxy)-L-aspartic acid

2(S)-Amino-3(S)-(benzoyloxy)succinic acid



C11-H11-N-O6; Mol wt: 253.21

ACTION – Agent for the treatment of neuropathies and neurodegenerative diseases such as epilepsy, Huntington’s disease, amyotrophic lateral sclerosis and Alzheimer’s disease that acts by inhibiting glutamate uptake activity of L-glutamate transporters. Compound was found to inhibit glutamate uptake in *Xenopus* oocytes expressing the bovine glutamate transporter gene B6LAST (79% inhibition at 100 μM). Contrary to glutamate, compound did not induce any inward current in oocytes expressing BGLAST at 100 μM; in addition, when added simultaneously with glutamate (both at 100 μM), it reduced the inward current induced by glutamate uptake by 50%. Other compounds from this series of β-hydroxyaspartic acid derivatives include the following:



Compound	R1	Formula
265394	1-Naph	C15H13NO6
265395	2-Naph	C15H13NO6

SOURCE – Suntory.

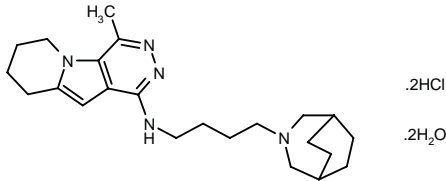
REFERENCES

1. Shimamoto, K. et al. (Suntory, Ltd.) *β-Hydroxyaspartic acid derivs.* EP 844234.

COGNITION-ENHANCING DRUGS

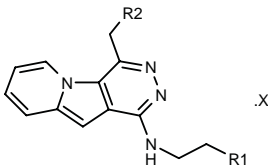
264067

N-[4-(3-Azabicyclo[3.2.2.]non-3-yl)butyl]-*N*-(4-methyl-6,7,8,9-tetrahydropyridazino[4,5-*b*]indolizin-1-yl)amine dihydrochloride dihydrate

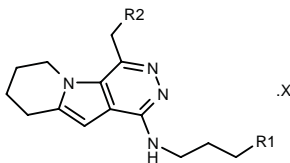


C23-H35-N5.2HCl.2H2O; Mol wt: 490.52

ACTION – Nootropic agent for the treatment of dementia such as senile dementia of the Alzheimer’s type that acts by virtue of its muscarinic M₁ receptor-agonist activity (101% inhibition of [³H]-pirenzepine binding in rat brain cortex at 1 μM; 102.5% stimulation of phosphoinositide turnover at 10 μM in CHO cells expressing M₁ receptors); the selectivity for M₁ vs. M₂ receptors was demonstrated in binding studies (K_i M₁ = 1.34 nM vs. K_i M₂ = 13.35 nM; ratio M₂/M₁ = 10). Other specifically claimed saturated and unsaturated pyridazino[4,5-*b*]indolizines include the following:



Compound	R1	R2	X	Formula
264110	CH2N(Et)2	OMe	.2HCl .2H2O	C ₁₉ H ₂₇ N ₅ O .2HCl.2H ₂ O
264111	3-azabicyclo[3.2.2]-non-3-yl-CH2	OMe	.2HCl .H2O	C ₂₃ H ₃₁ N ₅ O .2HCl.H ₂ O
264112	3-azabicyclo[3.2.2]-non-3-yl-CH2CH2	OMe	.2HCl .H2O	C ₂₄ H ₃₃ N ₅ O .2HCl.H ₂ O
264113	4-(2-pyrimidinyl)-1-Piz	OCH2Ph	.3HCl .H2O	C ₂₈ H ₃₀ N ₈ O .3HCl.H ₂ O
264114	CH2N(Et)2	NH(CH2)3-N(Et)2	.4HCl .H2O	C ₂₅ H ₄₁ N ₇ .4HCl.H ₂ O



Compound	R1	R2	X	Formula
264115	N(Et)2	H	fumarate .H2O	C ₁₈ H ₂₉ N ₅ .C ₄ H ₄ O ₄ .H ₂ O
264116	3-azabicyclo-[3.2.2]non-3-yl	H	.2HCl .2H2O	C ₂₂ H ₃₃ N ₅ O .2HCl.2H ₂ O
264117	N(Et)2	OMe	.2HCl .H2O	C ₁₉ H ₃₁ N ₅ O .2HCl.H ₂ O
264118	3-azabicyclo-[3.2.2]non-3-yl-CH2	OMe	.2HCl .H2O	C ₂₄ H ₃₇ N ₅ O .2HCl.H ₂ O
264119	4-morpholinyl-CH2	OCH2Ph	.2HCl .H2O	C ₂₆ H ₃₅ N ₅ O ₂ .2HCl.H ₂ O

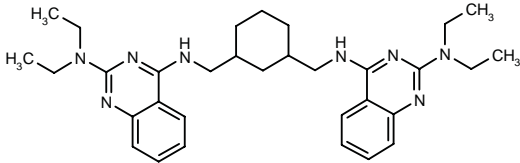
SOURCE – American Home Products.

REFERENCES

1. Sabb, A.L. (American Home Prods. Corp.) *Saturated and unsaturated pyridazino-[4,5-*b*]indolizines useful as antidementia agents*. US 5756501.

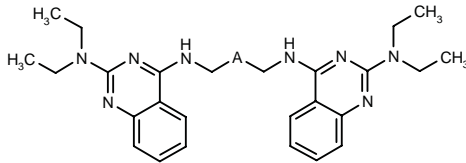
264477

N,N'-(Cyclohexene-1,3-diyl)bis(methylene)bis[2-(diethyl-amino)quinazoline-4-amine]



C32-H44-N8; Mol wt: 540.75

ACTION – Agent for the treatment of neurodegenerative diseases such as dementia, depression and myotonic dystrophy that acts on apamine-sensitive potassium channels, as demonstrated by its affinity for apamine binding sites in bovine cerebral membranes (K_i = 0.16 μM using [¹²⁵I]-apamine as the ligand). It inhibited Rb⁺ efflux in PC12 cells (80% inhibition at 10 μM). Within this series of 4,4'-bridged bis-2,4-diaminoquinazolines, the following are also included:



Compound	A	Formula
264928	-(CH2)3-	C ₂₉ H ₄₀ N ₈
264929	-CH2-	C ₂₇ H ₃₆ N ₈

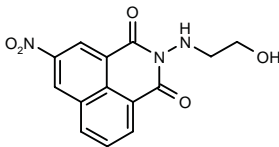
SOURCE – Bayer.

REFERENCES

1. Schohe-Loop, R. et al. (Bayer AG) *4,4'-Bridged bis-2,4-diaminoquinazolines*. US 5760230.

264866

2-(2-Hydroxyethylamino)-5-nitro-2,3-dihydro-1*H*-benz[*de*]isoquinoline-1,3-dione



C14-H11-N3-O5; Mol wt: 301.26

ACTION – Agent for the treatment of neurodegenerative disorders such as Alzheimer’s disease and epilepsy, as well as for the treatment of neuropathic pain and for repairing nervous system injury, that acts as an antagonist of neurotrophins such as nerve growth factor (NGF). Compound was shown to inhibit NGF-induced neurite outgrowth *in vitro* and was effective in several animal models of neuropathic pain.

Although neurotrophins function mainly to promote the survival of certain classes of peripheral and central neurons during development and following neuronal damage, they may also support inappropriate neurite outgrowth in some neurological disorders such as the sprouting of mossy fibers in epilepsy, the sprouting of sensory pain fibers in chronic pain syndromes and dystrophic neurite formation in Alzheimer's disease.

SOURCE – Allelix.

REFERENCES

1. Tehim, A. and Chen, X. (Allelix Biopharm., Inc.) *Neurotrophin antagonist compsns.* WO 9817278.

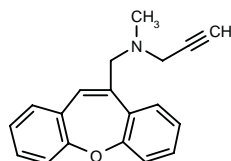
TREATMENT OF Cerebrovascular Diseases

CGP-3466

264482

N-(Dibenzo[*b,f*]oxepin-10-ylmethyl)-*N*-methyl-2-propynylamine

CGP-3466B (as maleate)



C19-H17-N-O; Mol wt: 275.35

ACTION – Potent, orally active neuroprotective and antiapoptotic agent, a structurally related analog of selegiline that is practically devoid of inhibitory activity against monoamine oxidase type B (MAO-B). Compound was effective in increasing the survival of CA1 hippocampal pyramidal cells in a model of hypoxia-ischemia ($ED_{50} < 0.3$ nmol/kg/day s.c., $ED_{50} < 1$ nmol/kg/day p.o.). In rat and mouse models of kainic acid-induced seizures, it prevented neuronal death at daily doses of 0.1 μ mol/kg s.c. or 0.1 mg/kg p.o. Both the free base and the maleate salt prevented p53-dependent apoptosis (cytosine arabinoside-induced apoptosis in rat cerebellar granule neurons) *in vitro*. Further *in vitro* studies indicated the involvement of an interaction with glyceraldehyde-3-phosphate dehydrogenase in its inhibition of apoptosis. Following oral administration, it increased the life span (30%) of mutant mice with progressive motor neuropathy.

SOURCE – Novartis.

REFERENCES

1. Kato, A.C. et al. *CGP3466B, a dibenzoxepine derivative, increases life-span in an animal model of motoneuron disease.* Soc Neurosci Abst 1997, 23(1): Abst 215.14.
2. Kragten, E. et al. *Glyceraldehyde-3-phosphate dehydrogenase, the putative target of the antiapoptotic compounds CGP 3466 and R-(–)-deprenyl.* J Biol Chem 1998, 273(10): 5821.
3. Paterson, I.A. et al. *CGP3466 and CGP3466B prevent cytosine arabinoside-induced apoptosis in cultures of cerebellar neurones.* J Neurochem 1998, 70(Suppl. 1): S11.

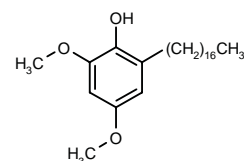
4. Paterson, I.A. et al. *CGP3466 prevents neuronal death in models of ischaemia and seizure in vivo.* J Neurochem 1998, 70(Suppl. 1): S11.

5. Zimmermann, K. et al. *Synthesis of tools for target identification of the anti-apoptotic compound CGP 3466; Part I.* Bioorg Med Chem Lett 1998, 8(10): 1195.

PHAFFIAOL

264499

2-Heptadecyl-4,6-dimethoxyphenol



C25-H44-O3; Mol wt: 392.62

Colorless crystalline powder, m.p. 74.8-77.3 °C.

ACTION – Antioxidant isolated from the red yeast *Phaffia rhodozyma* ATCC 24201; its *in vitro* antioxidant activity was nearly equivalent to that of α -tocopherol, as demonstrated against *tert*-butylhydroperoxide-initiated lipid peroxidation of rabbit erythrocyte ghost membranes. Potentially useful in the treatment of disorders in which active oxygen species exert a pathogenic role such as cerebral ischemia, Parkinson's disease and cancer.

SOURCE – Nippon Suisan.

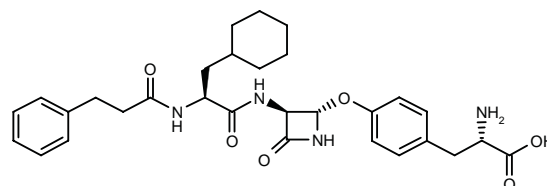
REFERENCES

1. Hata, K. (Nippon Suisan Co., Ltd.) *Novel phenol derivs.* JP 92145036.
2. Jinno, S. et al. *Phaffiaol, a new antioxidant isolated from a yeast Phaffia rhodozyma.* J Antibiot 1998, 51(5): 508.

MISCELLANEOUS NEUROLOGIC DRUGS

263891

4-*O*-[3(*S*)-[3-Cyclohexyl-2(*S*)-(3-phenylpropionamido)-propionyl]-4-oxoazetidin-2(*S*)-yl]-*L*-tyrosine



C30-H38-N4-O6; Mol wt: 550.65

ACTION – Agent for the treatment of muscular dystrophy, myocardial infarction, bone resorption, arthritis, cancer, pulmonary emphysema, septic shock, cerebral ischemia, Alzheimer's disease, cataracts, malaria, inflammation and bacterial, parasitic and viral infections, an inhibitor of cysteine proteases reported to exhibit improved plasma stability over related compounds. *In vitro*, compound inhibited cathepsin B and L with IC_{50} values of 34 and 1.82 μ M, respectively. It also inhibited cathepsin B and L activity (65 and 55% inhibition, respectively) after administration of 50 mg/kg i.p. to mice.

SOURCES – Natl. Res. Council Canada; Synphar.

REFERENCES

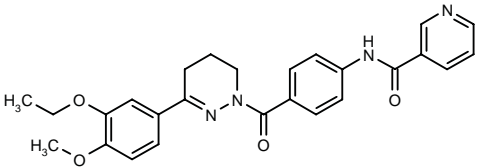
1. Singh, R. et al. (Synphar Labs., Inc.; Natl. Res. Council Canada) 4-Substd.-3-(2-amino-2-cycloalkyl methyl)-acetamido azetidin-2-one derivs. as cysteine proteinase regulators. WO 9812210.

RESPIRATORY DRUGS

ASTHMA THERAPY

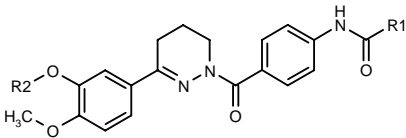
263253

N-[4-[3-(3-Ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydro-pyridazin-1-ylcarbonyl]phenyl]pyridine-3-carboxamide



C26-H26-N4-O4; Mol wt: 458.52

ACTION – Antiasthmatic, antiallergic and antiinflammatory agent, an inhibitor of phosphodiesterase type IV (PDE IV). Other specifically claimed arylalkanoyl pyridazines include the following:



Compound	R1	R2	Formula
263706	OEt	Et	C ₂₃ H ₂₇ N ₃ O ₅
263707	3-Pyr	cyclopentyl	C ₂₉ H ₃₀ N ₄ O ₄
263708	OEt	cyclopentyl	C ₂₆ H ₃₁ N ₃ O ₅
263709	4-Pyr	Et	C ₂₆ H ₂₈ N ₄ O ₄
263710	4-Pyr	cyclopentyl	C ₂₉ H ₃₀ N ₄ O ₄
263711	3-Pyr	Me	C ₂₅ H ₂₄ N ₄ O ₄
263712	OEt	Me	C ₂₂ H ₂₅ N ₃ O ₅

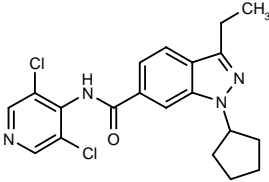
SOURCE – Merck KGaA.

REFERENCES

1. Rochus, J. et al. (Merck Patent GmbH) Arylalkanoyl pyridazines. WO 9806704.

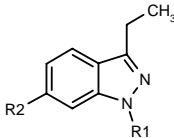
263803

1-Cyclopentyl-N-(3,5-dichloropyridin-4-yl)-3-ethyl-indazole-6-carboxamide



C20-H20-Cl2-N4-O; Mol wt: 403.31

ACTION – An inhibitor of phosphodiesterase type IV (PDE IV) and of the production of tumor necrosis factor (TNF), with potential in the treatment of a broad range of conditions including asthma, arthritis, septic shock, cachexia and AIDS. Other specifically claimed compounds from this series of substituted indazole derivatives include the following:



Compound	R1	R2	Formula
264679	cyclopentyl	2,6-(Cl)2-PhNHCO	C ₂₁ H ₂₁ Cl ₂ N ₃ O
264680	cyclobutyl	3,5-(Cl)2-4-Pyr-NHCO	C ₁₉ H ₁₈ Cl ₂ N ₄ O
264681	i-Pr	3,5-(Cl)2-4-Pyr-NHCO	C ₁₈ H ₁₈ Cl ₂ N ₄ O
264682	cyclopropyl-CH2	3,5-(Cl)2-4-Pyr-NHCO	C ₁₉ H ₁₈ Cl ₂ N ₄ O
264683	cyclohexyl	3,5-(Cl)2-4-Pyr-NHCO	C ₂₁ H ₂₂ Cl ₂ N ₄ O
264684	4-F-Ph	3,5-(Cl)2-4-Pyr-NHCO	C ₂₁ H ₁₅ Cl ₂ FN ₄ O
264685	cyclopentyl	CONHCH2CONHOH	C ₁₇ H ₂₂ N ₄ O ₃
264686	cyclopentyl	CONHCH2CH2SMe	C ₁₈ H ₂₅ N ₃ OS
264687	cyclopentyl	CON(Me)CH2CONHOH	C ₁₈ H ₂₄ N ₄ O ₃
264688	cyclopentyl	-CO-L-Ala-NHOCH2Ph	C ₂₅ H ₃₀ N ₄ O ₃
264689	cyclopentyl	-CO-D-Ala-NHOH	C ₁₈ H ₂₄ N ₄ O ₃
264690	cyclopentyl	2-thienyl	C ₁₈ H ₂₀ N ₂ S
264691	cyclopentyl	Ph	C ₂₀ H ₂₂ N ₂

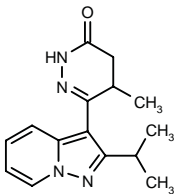
SOURCE – Pfizer.

REFERENCES

1. Marfat, A. (Pfizer, Inc.) Indazole derivs. and their use as inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF). WO 9809961.

264413

6-(2-Isopropylpyrazolo[1,5-a]pyridin-3-yl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one



C15-H18-N4-O; Mol wt: 270.33

SOURCES – Natl. Res. Council Canada; Synphar.

REFERENCES

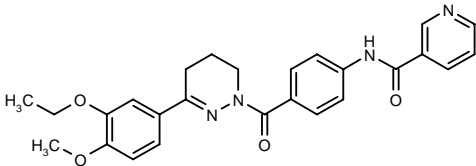
1. Singh, R. et al. (Synphar Labs., Inc.; Natl. Res. Council Canada) *4-Substd.-3-(2-amino-2-cycloalkyl methyl)-acetamido azetidin-2-one derivs. as cysteine proteinase regulators.* WO 9812210.

RESPIRATORY DRUGS

ASTHMA THERAPY

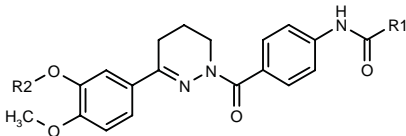
263253

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C26-H26-N4-O4; Mol wt: 458.52

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263709	4-Pyr	Et	C ₂₆ H ₂₈ N ₄ O ₄
263710	4-Pyr	cyclopentyl	C ₂₉ H ₃₀ N ₄ O ₄
263711	3-Pyr	Me	C ₂₅ H ₂₄ N ₄ O ₄
263712	OEt	Me	C ₂₂ H ₂₅ N ₃ O ₅

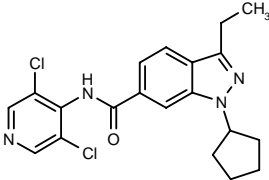
SOURCE – Merck KGaA.

REFERENCES

1. Rochus, J. et al. (Merck Patent GmbH) *Arylalkanoyl pyridazines.* WO 9806704.

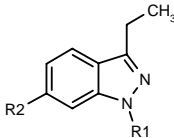
263803

1-Cyclopentyl-*N*-(3,5-dichloropyridin-4-yl)-3-ethyl-indazole-6-carboxamide



C20-H20-Cl2-N4-O; Mol wt: 403.31

ACTION – An inhibitor of phosphodiesterase type IV (PDE IV) and of the production of tumor necrosis factor (TNF), with potential in the treatment of a broad range of conditions including asthma, arthritis, septic shock, cachexia and AIDS. Other specifically claimed compounds from this series of substituted indazole derivatives include the following:



Compound	R1	R2	Formula
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264680	cyclobutyl	3,5-(Cl)2-4-Pyr-NHCO	C ₁₉ H ₁₈ Cl ₂ N ₄ O
264681	i-Pr	3,5-(Cl)2-4-Pyr-NHCO	C ₁₈ H ₁₈ Cl ₂ N ₄ O
264682	cyclopropyl-CH2	3,5-(Cl)2-4-Pyr-NHCO	C ₁₉ H ₁₈ Cl ₂ N ₄ O
264683	cyclohexyl	3,5-(Cl)2-4-Pyr-NHCO	C ₂₁ H ₂₂ Cl ₂ N ₄ O
264684	4-F-Ph	3,5-(Cl)2-4-Pyr-NHCO	C ₂₁ H ₁₅ Cl ₂ FN ₄ O
264685	cyclopentyl	CONHCH2CONHOH	C ₁₇ H ₂₂ N ₄ O ₃
264686	cyclopentyl	CONHCH2CH2SMe	C ₁₈ H ₂₅ N ₃ OS
264687	cyclopentyl	CON(Me)CH2CONHOH	C ₁₈ H ₂₄ N ₄ O ₃
264688	cyclopentyl	-CO-L-Ala-NHOCH2Ph	C ₂₅ H ₃₀ N ₄ O ₃
264689	cyclopentyl	-CO-D-Ala-NHOH	C ₁₈ H ₂₄ N ₄ O ₃
264690	cyclopentyl	2-thienyl	C ₁₈ H ₂₀ N ₂ S
264691	cyclopentyl	Ph	C ₂₀ H ₂₂ N ₂

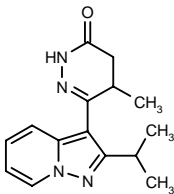
SOURCE – Pfizer.

REFERENCES

1. Marfat, A. (Pfizer, Inc.) *Indazole derivs. and their use as inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF).* WO 9809961.

264413

6-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one



C15-H18-N4-O; Mol wt: 270.33

ACTION – Bronchodilator, a phosphodiesterase (PDE) inhibitor with selectivity for respiratory tract enzymes, giving IC₅₀ values of 4, 5 and 0.1 µg/ml, respectively, for PDE III, IV and V from guinea pig respiratory tract.

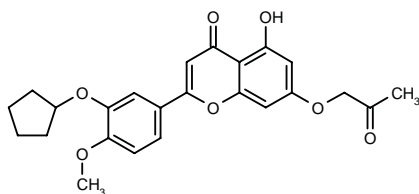
SOURCE – Kyorin.

REFERENCES

1. Kouno, Y. et al. (Kyorin Pharm. Co., Ltd.) *Pyrazolopyridylpyridazinone derivs. and process for the preparation thereof*. WO 9814448.

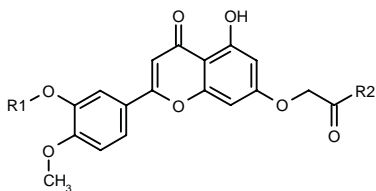
264660

2-(3-Cyclopentyloxy-4-methoxyphenyl)-5-hydroxy-7-(2-oxopropoxy)-4*H*-1-benzopyran-4-one



C24-H24-O7; Mol wt: 424.45

ACTION – An inhibitor of phosphodiesterase type IV (PDE IV) with potential in the treatment of asthma, rhinitis, acute respiratory distress syndrome (ARDS), dermatitis, psoriasis, rheumatoid arthritis, osteoarthritis, autoimmune diseases, multiple sclerosis, glomerulonephritis, septic shock, AIDS, depression and neurodegenerative disorders. Other specifically claimed compounds from this series of flavone derivatives include the following:



Compound	R1	R2	Formula
264914	cyclopentyl	OEt	C ₂₅ H ₂₆ O ₈
264915	cyclopentyl	N(Me) ₂	C ₂₅ H ₂₇ NO ₇
264916	cyclopentyl	N(Me)OMe	C ₂₅ H ₂₇ NO ₈
264917	cyclopentyl	NHMe	C ₂₄ H ₂₅ NO ₇
264918	exo-bicyclo[2.2.1]hept-2-yl	N(Me) ₂	C ₂₇ H ₂₉ NO ₇

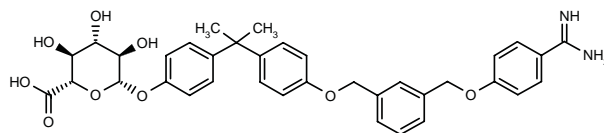
SOURCE – ADIR.

REFERENCES

1. Dhainaut, A. et al. (ADIR et Cie.) *Flavon derivs., process for their preparation, and pharmaceutical compsns. containing them*. EP 832886, JP 98114766.

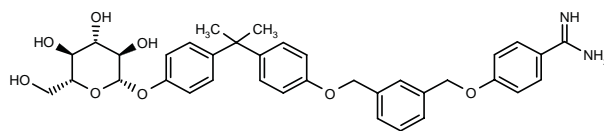
263863

1-O-[4-[1-[4-[3-(4-Amidinophenoxymethyl)benzyloxy]phenyl]-1-methylethyl]phenyl]-β-D-glucopyranuronic acid



C36-H38-N2-O9; Mol wt: 642.70

ACTION – Agent for the treatment of inflammatory disorders such as asthma, arthritis, psoriasis and ulcerative colitis with LTB₄ receptor-antagonist activity, as demonstrated in a binding assay (K_i = 1.0 nM). Another specifically claimed compound from this series of pyranoside derivatives is:



265356: C36-H40-N2-O8

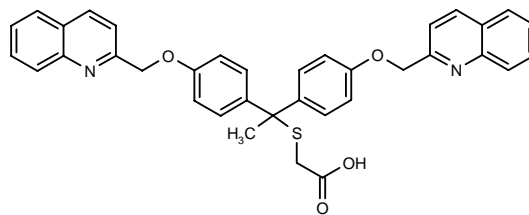
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Anderskewitz, R. et al. (Boehringer Ingelheim Int. GmbH; Boehringer Ingelheim Pharma KG) *Novel pyranoside derivs*. WO 9811119.

264405

2-[1,1-Bis[4-(2-quinolylmethoxy)phenyl]ethylsulfanyl]-acetic acid



C36-H30-N2-O4-S; Mol wt: 586.70

ACTION – Agent for the treatment of inflammatory disorders that acts by inhibiting 5-lipoxygenase and leukotriene biosynthesis. Compound inhibited LTB₄ production *in vitro* in human polymorphonuclear leukocytes (PMNLs) stimulated with calcium ionophore (IC₅₀ = 0.23 µM) and was active in a model of pleural inflammation induced by calcium ionophore A23187 in rats (ED₅₀ = 1.1 mg/kg p.o.).

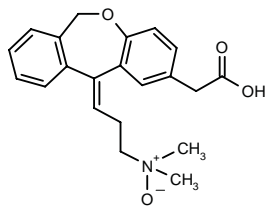
SOURCE – Abbott.

REFERENCES

1. Kolasa, T. et al. (Abbott Labs.) *Heteroarylmethoxyphenylthioalkyl carboxylates as inhibitors of leukotriene biosynthesis*. US 5783586, WO 9814429.

260542

2-[11(*Z*)-[3-(Dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl]acetic acid *N*-oxide



C21-H23-N-O4; Mol wt: 353.42

ACTION – Antiallergic agent that exhibited potent activity in the passive cutaneous anaphylaxis test in rats (ID₅₀ = 0.62 mg/kg i.v.) and against histamine-induced bronchoconstriction in guinea pigs (ID₅₀ = 0.17 mg/kg i.v.).

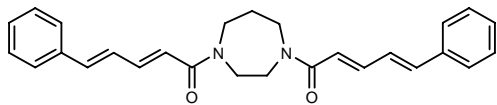
SOURCE – Kyowa Hakko.

REFERENCES

1. Oshima, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Antiallergic agents*. JP 98025241.

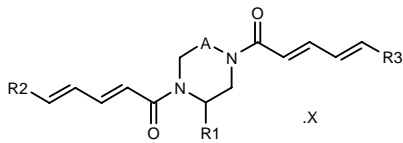
263294

1,4-Bis[5-phenyl-2(*E*),4(*E*)-pentadienyl]perhydro-1,4-diazepine

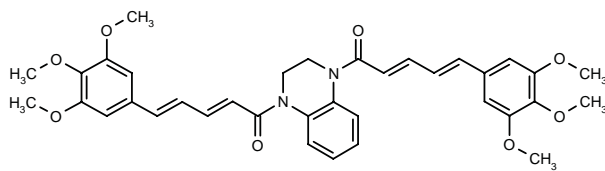


C27-H28-N2-O2; Mol wt: 412.53

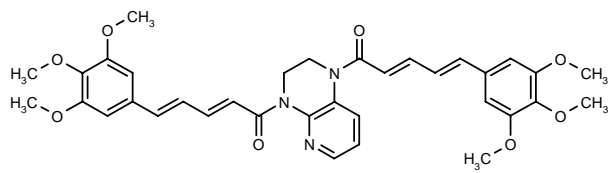
ACTION – Antiallergic agent proven to provide 100% inhibition of IgE antibody production in murine spleen B-cells stimulated with IL-4 and lipopolysaccharide (LPS) at 10 μM. Within this series of diamide derivatives, the following are also included:



Compound	R1	R2=R3	A	X	Formula
263699	H	3,4,5-(MeO)3-Ph	-(CH2)2-		C ₃₃ H ₄₀ N ₂ O ₈
263700	H	8-quinolinyl	-(CH2)2-		C ₃₃ H ₃₀ N ₄ O ₂
263701	H	3,4,5-(MeO)3-Ph	-CH2-		C ₃₂ H ₃₈ N ₂ O ₈
263702	CH2N(Me)2	3,4,5-(MeO)3-Ph	-CH2-	HCl	C ₃₅ H ₄₆ N ₃ O ₈ HCl
264795	H	2-Pyr	-(CH2)2-		C ₂₅ H ₂₆ N ₄ O ₂
264796	H	8-quinolinyl	-CH2-		C ₃₂ H ₂₈ N ₄ O ₂
264797	CO2H	3,4,5-(MeO)3-Ph	-CH2-		C ₃₃ H ₃₈ N ₂ O ₁₀



263703: C36-H38-N2-O8



264798: C35-H37-N3-O8

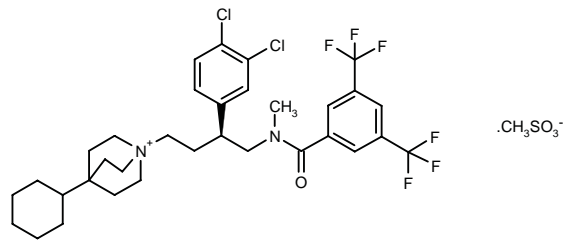
SOURCE – Kowa.

REFERENCES

1. Ishiwata, H. et al. (Kowa Co., Ltd.) *Diamide cpds. and drugs containing the same*. WO 9807702.

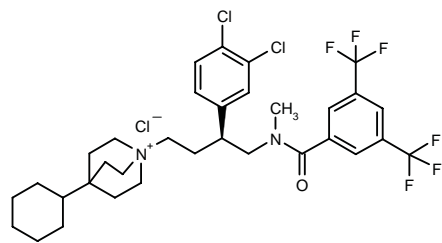
263305

4-Cyclohexyl-1-[3(*S*)-(3,4-dichlorophenyl)-4-[*N*-methyl-3,5-bis(trifluoromethyl)benzamido]butyl]quinuclidinium methanesulfonate



C33-H39-Cl2-F6-N2-O.C-H3-O3-S; Mol wt: 759.67

ACTION – Tachykinin receptor antagonist with good activity against both NK₁ and NK₂ receptors. Potentially useful for the treatment of inflammatory disorders such as asthma, arthritis and psoriasis, as well as CNS and gastrointestinal disorders, emesis, cough, acute or chronic pain and migraine. Another representative quaternary ammonium compound is:



264061: C33-H39-Cl2-F6-N2-O.Cl

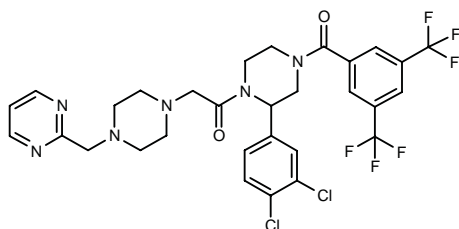
SOURCE – Pfizer.

REFERENCES

1. Monaghan, S.M. et al. (Pfizer, Ltd.; Pfizer, Inc.) *Quaternary ammonium cpds. as tachykinin antagonist*. WO 9807722.

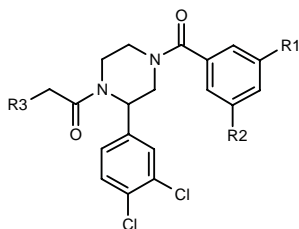
263348

4-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dichlorophenyl)-1-[2-[4-(2-pyrimidinylmethyl)piperazin-1-yl]acetyl]-piperazine



C30-H28-Cl2-F6-N6-O2; Mol wt: 689.49

ACTION – Agent for the treatment of chronic airways diseases such as asthma that acts by virtue of its neurokinin receptor-antagonist activity, demonstrating affinity for both NK₁ and NK₂ receptors (K_i = 23.3 and 29.1 nM, respectively, in isolated guinea pig vas deferens and hamster trachea preparations). Other representative compounds within this series of piperazino derivatives include the following:



Compound	R1=R2	R3	Isomer	Formula
264301	CF ₃	4-(1,3-benzodioxol-5-yl-CH ₂)-1-Piz		C ₃₃ H ₃₀ Cl ₂ F ₆ N ₄ O ₄
264302	CF ₃	4-(1-Pip)-1-Pip		C ₃₁ H ₃₄ Cl ₂ F ₆ N ₄ O ₂
264303	CF ₃	4-(2-oxo-2,3-dihydro-1-benzimidazolyl)-1-Pip		C ₃₃ H ₂₉ Cl ₂ F ₆ N ₅ O ₃
264304	Me	4-Ph-cyclohexyl-NH		C ₃₃ H ₃₇ Cl ₂ N ₃ O ₂
264305	Me	4-(PhCH ₂)-1-Pip-CH ₂		C ₃₄ H ₃₉ Cl ₂ N ₃ O ₂
264306	Me	4-(PhCH ₂)-1-Piz-CH ₂	B	C ₃₃ H ₃₈ Cl ₂ N ₄ O ₂
264307	Me	4-(PhCH ₂)-1-Piz-CH ₂	racemic	C ₃₃ H ₃₈ Cl ₂ N ₄ O ₂

SOURCE – Schering Corp.

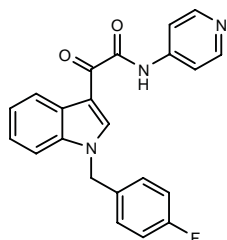
REFERENCES

1. Shue, H.-J. et al. (Schering Corp.) *Piperazino derivs. as neurokinin antagonists*. WO 9808826.

263797

2-[1-(4-Fluorobenzyl)indol-3-yl]-2-oxo-N-(4-pyridyl)-acetamide

2-[1-(4-Fluorobenzyl)indol-3-yl]-N-(4-pyridyl)glyoxylamide



C22-H16-F-N3-O2; Mol wt: 373.39

ACTION – Antiasthmatic, antiallergic and immunosuppressive agent proven to inhibit ovalbumin-induced eosinophil infiltration into bronchoalveolar lavage (BAL) by 55.4 and 56.1% at 10 mg/kg i.p. and 30 mg/kg p.o., respectively, 24 h after challenge, being similar in potency to ciclosporin (47.0 and 68.8% inhibition, respectively, at the same doses). Compound was also shown to inhibit lymphocyte activation and proliferation.

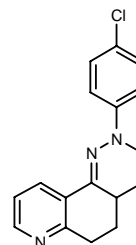
SOURCE – Asta Medica.

REFERENCES

1. Lebaut, G. et al. (Asta Medica AG) *N-Substd. indol-3-glyoxylamid with antiasthmatic, antiallergic and immunosuppressive/immunomodulating effect*. WO 9809946.

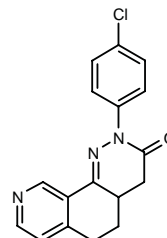
263807

2-(4-Chlorophenyl)-2,3,4,4a,5,6-hexahydropyrido[2,3-*h*]-cinnoline



C17-H16-Cl-N3; Mol wt: 297.79

ACTION – Antiasthmatic, antiallergic and antiinflammatory agent from a series of arylpyridazines, wherein the following is also included:



264692: C17-H14-Cl-N3-O

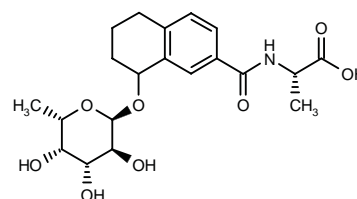
SOURCE – Astra.

REFERENCES

1. Bantick, J. et al. (Astra Pharm. Ltd.; Astra AB) *Novel aryl-pyridazines*. WO 9809969.

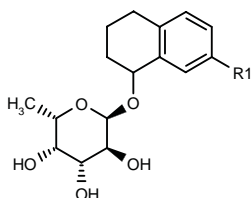
263811

N-[8-(6-Deoxy-α-L-galactopyranosyloxy)-5,6,7,8-tetrahydronaphthalen-2-ylcarbonyl]-L-alanine



C20-H27-N-O8; Mol wt: 409.44

ACTION – Cell adhesion inhibitor that acts by inhibiting the binding of selectins to sialyl Lewis X (SLe^x), potentially useful for the treatment of a broad range of conditions characterized by cell adhesion including asthma, ARDS, inflammatory bowel disease, psoriasis, rheumatoid arthritis, reperfusion injury and septic shock. Other specifically claimed compounds from this series of tetrahydronaphthalene derivatives include the following:



Compound	R1	Formula
265166	-CO-D-Ala-OH	C ₂₀ H ₂₇ NO ₈
265167	CO ₂ H	C ₁₇ H ₂₂ O ₇
265168	(CH ₂) ₃ CO ₂ H	C ₂₀ H ₂₆ O ₇
265169	CH ₂ C(Me) ₂ CH(Me)CO ₂ H	C ₂₃ H ₃₄ O ₇
265170	CONHCH ₂ CO ₂ H	C ₁₉ H ₂₅ NO ₈
265171	-CO-L-Pro-OH	C ₂₂ H ₂₉ NO ₈

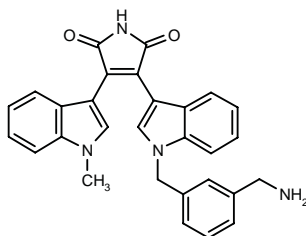
SOURCE – Chiroscience.

REFERENCES

1. Taylor, R.J.K. et al. (Chiroscience, Ltd.) *Tetrahydronaphthalene derivs. and their therapeutic use*. WO 9809977.

263856

3-[1-[3-(Aminomethyl)benzyl]indol-3-yl]-4-(1-methylindol-3-yl)-2,5-dihydro-1H-pyrrole-2,5-dione



C29-H24-N4-O2; Mol wt: 460.53

ACTION – Protein kinase C (PKC) inhibitor with potential in the treatment of inflammatory and immunological disorders such as asthma, bronchitis, rhinitis, atopic dermatitis, psoriasis, inflammatory bowel disease and rheumatoid arthritis. Compound is active topically and is reported to have the potential to be deactivated systemically, being rapidly metabolized to less active compounds, thus being less likely to be associated with severe systemic side effects. Preferably for administration via inhalation.

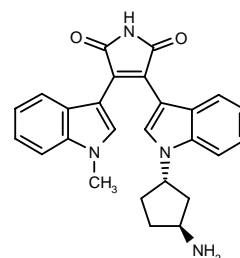
SOURCE – Astra.

REFERENCES

1. Bergstrand, H. et al. (Astra AB) *New pharmaceutically active cpds*. WO 9811102.

263857

(1S,3S)-3-[1-(3-Aminocyclopentyl)indol-3-yl]-4-(1-methylindol-3-yl)-2,5-dihydro-1H-pyrrole-2,5-dione



C26-H24-N4-O2; Mol wt: 424.50

ACTION – Protein kinase C (PKC) inhibitor with potential in the treatment of inflammatory and immunological disorders such as asthma, bronchitis, rhinitis, atopic dermatitis, psoriasis, inflammatory bowel disease and rheumatoid arthritis, as well as cancer. Suitable for topical and oral administration.

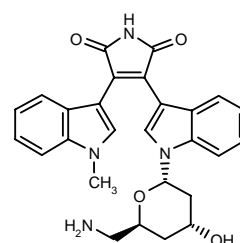
SOURCE – Astra.

REFERENCES

1. Bergstrand, H. et al. (Astra AB) *New pharmaceutically active cpds*. WO 9811103.

263858

3-[1-(6-Amino-2,4,6-trideoxy-α-D-threo-hexopyranosyl)indol-3-yl]-4-(1-methylindol-3-yl)-2,5-dihydro-1H-pyrrole-2,5-dione



C27-H26-N4-O4; Mol wt: 470.53

ACTION – Protein kinase C (PKC) inhibitor with potential in the treatment of inflammatory and immunological disorders such as asthma, bronchitis, rhinitis, atopic dermatitis, psoriasis, inflammatory bowel disease and rheumatoid arthritis, as well as cancer. Suitable for topical and oral administration.

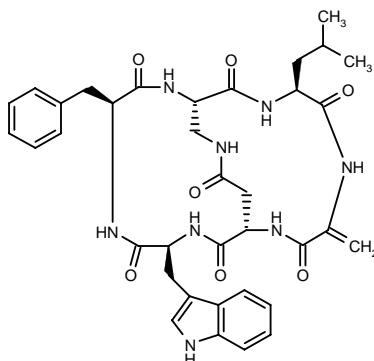
SOURCE – Astra.

REFERENCES

1. Bergstrand, H. et al. (Astra AB) *New pharmaceutically active cpds*. WO 9811105.

264488

Cyclo[dehydroalanine-L-aspartyl-L-tryptophyl-L-phenylalanyl-2(S),3-diaminopropionyl-L-leucine] C-4.2-N-3.5-lactam



C36-H42-N8-O7; Mol wt: 698.78

ACTION – Highly potent and competitive tachykinin NK₂ receptor antagonist proven effective *in vitro* in antagonizing an NK₂ receptor-mediated response ($pA_2 = 9.65 \pm 0.02$ for inhibition of rat vas deferens smooth muscle contractions induced by the NK₂ agonist β -Ala⁸-NKA[4-10]; $pA_2 = 8.25 \pm 0.04$ and 8.21 ± 0.04 , respectively, for the selective NK₂ receptor antagonists Neuronorm and MEN-10627). Potentially useful as a lead compound for the development of drugs for the treatment of diseases where NK₂ receptors may be involved, including asthma.

SOURCES – Univ. Napoli “Federico II”, Naples (IT); Seconda Univ. Napoli, Naples (IT).

REFERENCES

1. Lombardi, A. et al. A novel super-potent neurokinin A receptor antagonist containing dehydroalanine. *Bioorg Med Chem Lett* 1998, 8(10): 1153.

INTERLEUKIN-13 BINDING PROTEIN**263819**

IL-13BP

ACTION – High-affinity binding protein for IL-13 identified in mammalian body fluids that is capable of interacting with IL-13 or a related cytokine with greater affinity than soluble IL-13 receptor α -chain (IL-13R α) and acts as a potent antagonist of IL-13 activity. Claimed for use in the treatment of allergic conditions.

SOURCE – Amrad.

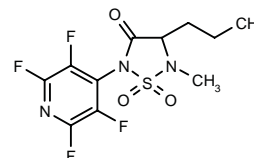
REFERENCES

1. Nicola, N.A. et al. (Amrad Operations Pty., Ltd.) *Therapeutic molecules*. WO 9810638.

TREATMENT OF RDS AND EMPHYSEMA

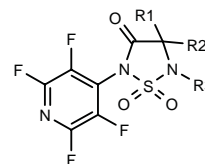
263487

5-Methyl-4-propyl-2-(2,3,5,6-tetrafluoro-4-pyridyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide



C11-H11-F4-N3-O3-S; Mol wt: 341.28

ACTION – Agent for the treatment of degenerative diseases such as emphysema, rheumatoid arthritis and pancreatitis, an inhibitor of serine proteases with a K_i of 10 nM when tested *in vitro* for its inhibitory effect on human leukocyte elastase. A specifically claimed compound within a series of 2-(2,3,5,6-tetrafluoro-4-pyridyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
263614	i-BuCH ₂	H	Me	C ₁₃ H ₁₅ F ₄ N ₃ O ₃ S
263615	Me	Me	Me	C ₁₀ H ₉ F ₄ N ₃ O ₃ S
263616	CH ₂ Ph	H	H	C ₁₄ H ₉ F ₄ N ₃ O ₃ S

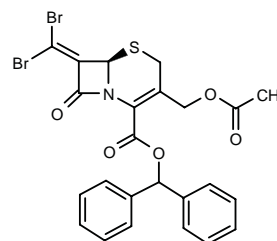
SOURCE – Sanofi.

REFERENCES

1. Desai, R.C. (Sanofi Winthrop, Inc.) 2-(2,3,5,6-Tetrafluoro-4-pyridyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxides and compns. and method of use thereof. US 5750546.

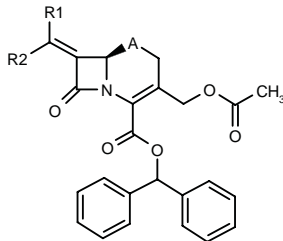
264469

(6R)-3-(Acetoxymethyl)-7-(dibromomethylene)-3-cephem-4-carboxylic acid diphenylmethyl ester



C24-H19-Br2-N-O5-S; Mol wt: 593.29

ACTION – Agent for the treatment of inflammatory and degenerative diseases such as emphysema, acute respiratory distress syndrome (ARDS), atherosclerosis and rheumatoid arthritis, an inhibitor of human leukocyte elastase (HLE; IC₅₀ = 0.26 μM) and to a lesser extent of porcine pancreatic elastase (PPE; IC₅₀ = 6.42 μM). Other compounds from this series of 7-alkylidene cephalosporins include the following:



Compound	R1	R2	A	Formula
264944	Br	Br	SO2	C ₂₄ H ₁₉ Br ₂ NO ₇ S
264945	H	Br	S	C ₂₄ H ₂₀ BrNO ₅ S
264946	Cl	Cl	S	C ₂₄ H ₁₉ Cl ₂ NO ₅ S
264947	CO ₂ Me	H	S	C ₂₈ H ₂₃ NO ₇ S

SOURCE – Research Corporation Technologies.

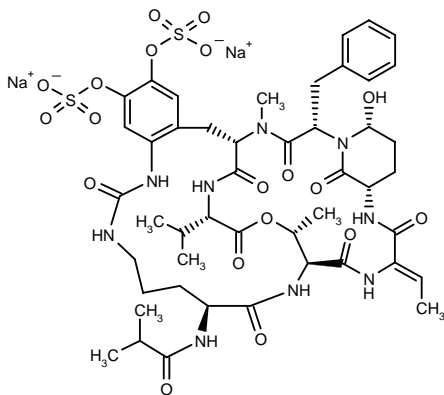
REFERENCES

1. Buynak, J.D. et al. (Res. Corp. Technol., Inc.) *Use of 7-alkylidene cephalosporins to inhibit elastase activity.* US 5760027.

FR-134043

194175

(1*S*,15*S*,18*S*,21*Z*,24*S*,27*R*,29*S*,34*S*,37*R*)-29-Benzyl-21-ethylidene-27-hydroxy-15-(isobutyramido)-34-isopropyl-31,37-dimethyl-5,6-bis(sulfooxy)-36-oxa-9,11,17,20,23,28,31,33-octaazatetracyclo-[16.13.6.1^{24,28}.0^{3,8}]octatriaconta-3,5,7-triene-10,16,19,22,30,32,35,38-octaone disodium salt



C47-H61-N9-Na2-O19-S2; Mol wt: 1166.15

ACTION – A potent, water-soluble human neutrophil elastase (HNE) inhibitor (K_i = 8 nM), a derivative of FR-901277⁺ (WS-7622A⁺⁺), a natural elastase inhibitor isolated from cultures of *Streptomyces resistomycificus*. Compound inhibited both HNE and porcine pancreatic elastase (PPE) activity (IC₅₀ = 35 and 49 nM, respectively). It protected against HNE-induced lung hemorrhage in hamsters both by intratracheal and i.v. administration, with ED₅₀ values of 3.1 μg/animal and 5.0 mg/kg, respectively; it had lower potency in protecting

against PPE-induced emphysema in hamsters (ED₅₀ = 1590 μg/animal intratracheally). Subcutaneous treatment suppressed HNE-induced paw edema in mice (ED₅₀ = 3.3 mg/kg at 4 h after elastase injection), and an i.v. infusion (0.25 mg/kg/h) improved lipopolysaccharide (LPS)-induced thrombocytopenia and certain coagulation parameters in rats.

SOURCE – Fujisawa.

REFERENCES

1. Inamura, N. et al. (Fujisawa Pharm. Co., Ltd.) *A prophylactic/therapeutic compsn. containing WS7622A for preventing or treating disseminated intravascular coagulation, chronic respiratory tract infectious disease or chronic bronchitis.* EP 519354, JP 93221872.

2. Fujikawa, A. et al. *Conformational study of FR134043, a novel inhibitor of human leukocyte elastase.* Pept Chem 1995 (Pub. 1996): 437.

3. Shinguh, Y. et al. *Pharmacological properties of a novel and potent elastase inhibitor FR134043.* Jpn J Pharmacol 1993, 61(Suppl. I): Abst O-222.

4. Shinguh, Y. et al. *Biochemical and pharmacological characterization of FR134043, a novel elastase inhibitor.* Eur J Pharmacol 1998, 345(2): 299.

*Drug Data Rep 1993, 15(8): 723.

**Drug Data Rep 1992, 14(7): 586.

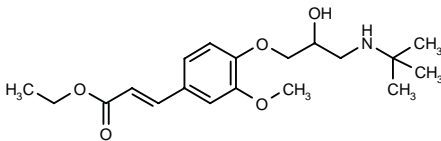
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

FERULINOLOL

265413

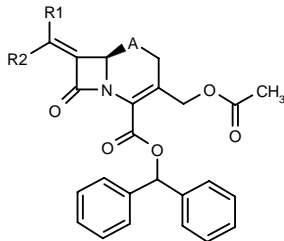
(±)-3-[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-methoxyphenyl]-2(*E*)-propenoic acid ethyl ester



C19-H29-N-O5; Mol wt: 351.44

ACTION – Selective β₁-adrenoceptor antagonist (K_i = 103 nM in rat ventricular membranes) with partial β₂-adrenoceptor-agonist activity (K_i = 2412 nM in rat lung membranes) and devoid of α-adrenoceptor-blocking activity. Doses of 0.1-1.0 mg/kg i.v. in rats produced dose-dependent bradycardia without alterations in blood pressure. Ferulinolol inhibited isoproterenol-induced tachycardia but did not block the pressor response to phenylephrine. In isolated guinea pig tissues, it antagonized the isoproterenol-induced positive chronotropic effect on right atria and positive inotropic effect on left atria (pA₂ = 7.62 and 7.54, respectively), whereas it was less potent in antagonizing isoproterenol-induced tracheal relaxation (pA₂ = 6.28; selectivity ratio β₁/β₂ = 21.9); in reserpine-treated guinea pig tracheal strips, it produced relaxation at 30 μM consistent with partial β₂-adrenoceptor-agonist activity. It has also demonstrated antioxidant properties. This profile is suggested to be associated with a reduced risk of asthma attacks in patients with bronchospastic disorders.

ACTION – Agent for the treatment of inflammatory and degenerative diseases such as emphysema, acute respiratory distress syndrome (ARDS), atherosclerosis and rheumatoid arthritis, an inhibitor of human leukocyte elastase (HLE; IC₅₀ = 0.26 μM) and to a lesser extent of porcine pancreatic elastase (PPE; IC₅₀ = 6.42 μM). Other compounds from this series of 7-alkylidene cephalosporins include the following:



Compound	R1	R2	A	Formula
264944	Br	Br	SO2	C ₂₄ H ₁₉ Br ₂ NO ₇ S
264945	H	Br	S	C ₂₄ H ₂₀ BrNO ₅ S
264946	Cl	Cl	S	C ₂₄ H ₁₉ Cl ₂ NO ₅ S
264947	CO ₂ Me	H	S	C ₂₈ H ₂₃ NO ₇ S

SOURCE – Research Corporation Technologies.

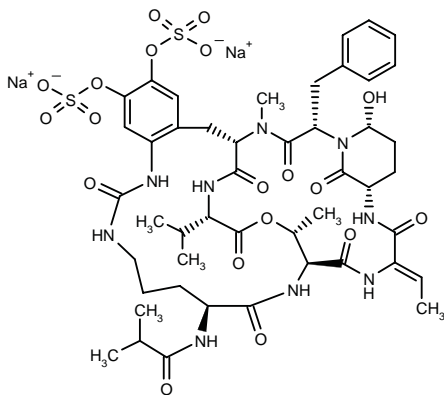
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FR-134043

194175

(1S,15S,18S,21Z,24S,27R,29S,34S,37R)-29-Benzyl-21-ethylidene-27-hydroxy-15-(isobutyramido)-34-isopropyl-31,37-dimethyl-5,6-bis(sulfooxy)-36-oxa-9,11,17,20,23,28,31,33-octaazatetracyclo-[16.13.6.1^{24,28}.0^{3,8}]octatriaconta-3,5,7-triene-10,16,19,22,30,32,35,38-octaone disodium salt



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against PPE-induced emphysema in hamsters (ED₅₀ = 1590 μg/animal intratracheally). Subcutaneous treatment suppressed HNE-induced paw edema in mice (ED₅₀ = 3.3 mg/kg at 4 h after elastase injection), and an i.v. infusion (0.25 mg/kg/h) improved lipopolysaccharide (LPS)-induced thrombocytopenia and certain coagulation parameters in rats.

SOURCE – Fujisawa.

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1. Inamura, N. et al. (Fujisawa Pharm. Co., Ltd.) A prophylactic/therapeutic compsn. containing WS7622A for preventing or treating disseminated intravascular coagulation, chronic respiratory tract infectious disease or chronic bronchitis. EP 519354, JP 93221872.

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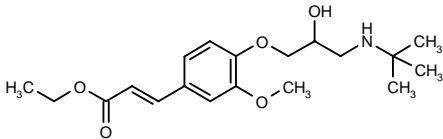
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

FERULINOLOL

265413

(±)-3-[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-methoxyphenyl]-2(*E*)-propenoic acid ethyl ester



C19-H29-N-O5; Mol wt: 351.44

ACTION – Selective β₁-adrenoceptor antagonist (K_i = 103 nM in rat ventricular membranes) with partial β₂-adrenoceptor-agonist activity (K_i = 2412 nM in rat lung membranes) and devoid of α-adrenoceptor-blocking activity. Doses of 0.1-1.0 mg/kg i.v. in rats produced dose-dependent bradycardia without alterations in blood pressure. Ferulinolol inhibited isoproterenol-induced tachycardia but did not block the pressor response to phenylephrine. In isolated guinea pig tissues, it antagonized the isoproterenol-induced positive chronotropic effect on right atria and positive inotropic effect on left atria (pA₂ = 7.62 and 7.54, respectively), whereas it was less potent in antagonizing isoproterenol-induced tracheal relaxation (pA₂ = 6.28; selectivity ratio β₁/β₂ = 21.9); in reserpine-treated guinea pig tracheal strips, it produced relaxation at 30 μM consistent with partial β₂-adrenoceptor-agonist activity. It has also demonstrated antioxidant properties. This profile is suggested to be associated with a reduced risk of asthma attacks in patients with bronchospastic disorders.

SOURCE – Kaohsiung Med. Coll., Kaohsiung (TW).

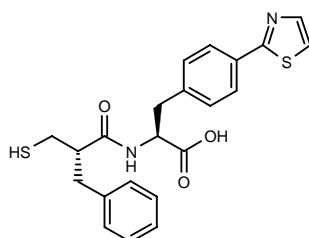
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1. Huang, Y.C. et al. *Ferulidilol: An α/β -adrenoceptor blocker, derived from ferulic acid, with antioxidant-associated cardioprotective activity*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 36.104.

2. Wu, B.-N. et al. *A highly selective β_1 -adrenergic blocker with partial β_2 -agonist activity derived from ferulic acid, an active component of Ligusticum wallichii Franch.* J Cardiovasc Pharmacol 1998, 31(5): 750.

264479

N-[2(*S*)-Phenyl-3-sulfanylpropionyl]-4-(2-thiazolyl)-*L*-phenylalanine



C22-H22-N2-O3-S2; Mol wt: 426.55

ACTION – Agent for the treatment of cardiovascular disorders, particularly hypertension, a dual inhibitor of angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) activity, with IC_{50} values of 3.2 (enzyme purified from rabbit lung) and 1.8 nM (rat kidney cortex homogenates), respectively.

SOURCE – Zambon.

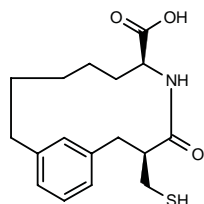
REFERENCES

1. Santangelo, F. et al. (Zambon Group SpA) *Thiol derivs. with metallopeptidase inhibitory activity*. US 5760241.

CGS-26582

264158

(3*S*,6*S*)-4-Oxo-3-(sulfanylmethyl)-5-azabicyclo-[10.3.1]hexadeca-1(16),12,14-triene-6-carboxylic acid



C17-H23-N-O3-S; Mol wt: 321.43

ACTION – A triple inhibitor of endothelin-converting enzyme (ECE), neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE), with IC_{50} values of 620, 4 and 175 nM, respectively. *In vivo*, at 30 mg/kg i.v. it inhibited the increase in blood pressure induced by ET-1 in rats by 44%. Further optimization of potency and duration of action is suggested to possibly lead to novel agents for the treatment of cardiovascular and renal diseases.

SOURCE – Novartis.

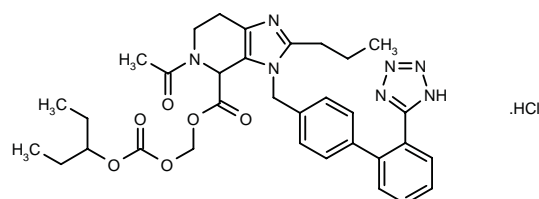
REFERENCES

1. Ksander, G.M. et al. *Benzofused macrocyclic lactams as triple inhibitors of endothelin-converting enzyme, neutral endopeptidase 24.11, and angiotensin-converting enzyme*. J Cardiovasc Pharmacol 1998, 31(Suppl. 1): S71.

TA-606*

229185

5-Acetyl-2-propyl-3-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine-4-carboxylic acid 3-pentyloxycarbonyloxymethyl ester hydrochloride



C33-H39-N7-O6.HCl; Mol wt: 666.18

ACTION – Potent, orally active, nonpeptide angiotensin II receptor antagonist, a prodrug of 606A⁺ with improved oral bioavailability relative to the active metabolite 606A in rats (1.2% and 13.6% for 606A and TA-606, respectively, at the dose of 3.0 mg/kg p.o.). It exhibited a potent (ED_{30} = 0.21 mg/kg p.o.) and long-lasting (> 24 h at 1 mg/kg p.o. and above) hypotensive effect in conscious spontaneously hypertensive rats, showing stronger activity than either 606A (ED_{30} = 1.8 mg/kg p.o.) or losartan (ED_{30} = 4.8 mg/kg p.o.), and similar results were obtained in conscious renal hypertensive rats (ED_{30} = 0.14 mg/kg p.o. for TA-606). Compound was not active in a model of non-renin-dependent hypertension (conscious DOCA-salt hypertensive rats). TA-606 (3-30 mg/kg/day p.o. x 12 days) attenuated the development of hypertension in stroke-prone spontaneously hypertensive rats, similar to the angiotensin-converting enzyme (ACE) inhibitor imidapril (3 mg/kg/day p.o. x 12 days), with no rebound effect following discontinuation. It has been proposed as a candidate for clinical trials in patients with hypertension.

SOURCE – Tanabe Seiyaku.

REFERENCES

1. Sekine, Y. et al. (Tanabe Seiyaku Co., Ltd.) *Imidazopyridine derivs. and process for preparing the same*. CA 2146802, EP 682023, JP 96003162, US 5753672.

2. Harada, Y. et al. *Pharmacological characterization of TA-606, a novel angiotensin II receptor antagonist-1. In vitro study*. Jpn J Pharmacol 1996, 71(Suppl. 1): Abst P-727.

3. Hashimoto, Y. et al. *Pharmacologic profile of TA-606, a novel angiotensin II-receptor antagonist in the rat*. J Cardiovasc Pharmacol 1998, 31(4): 568.

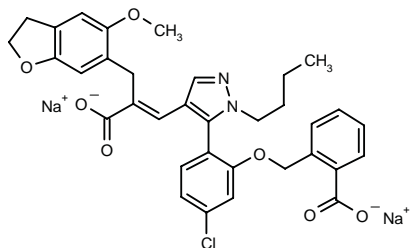
*Identified compound **229185** Annu Drug Data Rep 1996, 18(3): 236.

*Drug Data Rep 1995, 18(10): 906.

SB-247083

264274

3-[1-Butyl-5-[4-chloro-2-(2-carboxybenzyloxy)phenyl]-1*H*-pyrazol-4-yl]-2-(5-methoxy-2,3-dihydrobenzofuran-6-ylmethyl)-2(*E*)-propenoic acid disodium salt



C34-H31-Cl-N2-Na2-O7; Mol wt: 661.06

ACTION – Potent nonpeptide, orally active endothelin (ET) antagonist selective for ET_A receptors, with a K_i of 0.41 nM for [¹²⁵I]-ET-1 binding in membranes from CHO cells expressing cloned human ET_A receptors versus 467 nM for ET_B receptors. It also showed *in vitro* functional ET_A receptor antagonism, with a K_b of 3.5 ± 0.3 nM for ET-1-induced rat aortic contractions, and significantly less potent functional ET_B antagonism, with a K_b of 0.34 μM for sarafotoxin 6c-induced rabbit pulmonary artery contractions. Pharmacodynamic and pharmacokinetic studies in rats revealed that compound was effectively absorbed from the gastrointestinal tract, with a bioavailability of 46%, and intragastric administration (1-30 mg/kg) inhibited the systemic pressor actions of ET-1 for up to 8 h.

SOURCE – SmithKline Beecham.

REFERENCES

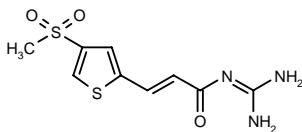
1. Douglas, S.A. et al. *Pharmacologic characterization of the novel, orally available endothelin-A-selective antagonist SB 247083*. J Cardiovasc Pharmacol 1998, 31(Suppl. 1): S273.

2. Willette, R.N. et al. *Plasma- and cerebrospinal fluid-immunoreactive endothelin-1: Effects of nonpeptide endothelin receptor antagonists with diverse affinity profiles for endothelin-A and endothelin-B receptors*. J Cardiovasc Pharmacol 1998, 31(Suppl. 1): S149.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

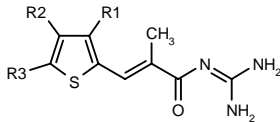
264054

N-[3-[4-(Methylsulfonyl)thien-2-yl]-2(*E*)-propenoyl]-guanidine



C9-H11-N3-O3-S2; Mol wt: 273.32

ACTION – An inhibitor of Na⁺/H⁺ exchange potentially useful for the treatment of myocardial ischemic disorders such as myocardial infarction and angina pectoris, as well as peripheral and cerebral ischemic disorders and proliferative disorders such as atherosclerosis, pulmonary, hepatic or renal fibrosis and prostatic hyperplasia. Other specifically claimed substituted thiophenylalkenylcarboxylic acid guanidines include the following:



Compound	R1	R2	R3	Formula
264634	H	H	Me	C ₁₀ H ₁₃ N ₃ OS
264635	H	H	SO ₂ Me	C ₁₀ H ₁₃ N ₃ O ₃ S ₂
264636	Cl	i-PrSO ₂	SMe	C ₁₃ H ₁₈ ClN ₃ O ₃ S ₃
264637	Cl	i-PrSO ₂	SO ₂ Me	C ₁₃ H ₁₈ ClN ₃ O ₅ S ₃

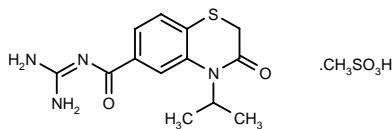
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Schwark, J.-R. et al. (Hoechst AG) *Subst. thiophenylalkenylcarboxylic acid guanidines, processes for their preparation, their use as a medicament or diagnostic, and a medicament containing them*. EP 790245, US 5756535.

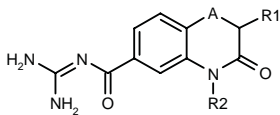
264388

*N*²-(4-Isopropyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-6-ylcarbonyl)guanidine methanesulfonate

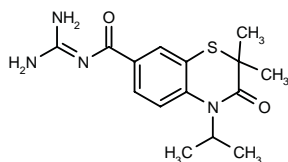


C13-H16-N4-O2-S.C-H4-O3-S; Mol wt: 388.46

ACTION – Inhibitor of Na⁺/H⁺ exchange, as demonstrated *in vitro* using rat platelet-rich plasma (IC₅₀ = 0.0091 μM). Potentially useful for the treatment or prevention of myocardial infarction, arrhythmia and angina pectoris. Within this series of benzo[1,4]thiazine derivatives, the following are also included:



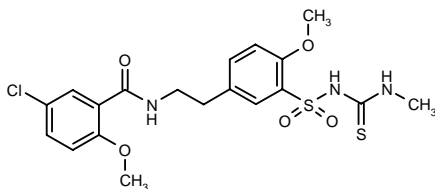
Compound	R1	R2	A	Formula
265400	H	i-Pr	S	C ₁₃ H ₁₈ N ₄ O ₂ S
265401	H	i-Pr	SO ₂	C ₁₃ H ₁₆ N ₄ O ₄ S
265402	H	Me	S	C ₁₁ H ₁₂ N ₄ O ₂ S
265403	H	Et	S	C ₁₂ H ₁₄ N ₄ O ₂ S
265404	H	H	S	C ₁₀ H ₁₀ N ₄ O ₂ S
265405	Me	i-Pr	S	C ₁₄ H ₁₈ N ₄ O ₂ S

**265406:** C15-H20-N4-O2-S**SOURCE** – Kanebo.**REFERENCES**

1. Yamamoto, T. et al. (Kanebo, Ltd.) *Benzo[1,4]thiazine derivs. and drugs comprising the same*. JP 98152481, WO 9813357.

ANTIARRHYTHMIC DRUGS**HMR-1883*****218761**

5-Chloro-2-methoxy-*N*-[2-[4-methoxy-3-(3-methylthio-ureidosulfonyl)phenyl]ethyl]benzamide



C19-H22-Cl-N3-O5-S2; Mol wt: 471.97

ACTION – Cardiosselective K_{ATP} channel blocker currently in phase I evaluation for ischemic ventricular arrhythmias and sudden cardiac death. Studies in isolated rat hearts subjected to ischemia and reperfusion showed that HMR-1883 concentration-dependently reduced postischemic ventricular fibrillation, and it also had a favorable effect on cell viability in postischemic recovery. The cardio-selectivity of HMR-1883 was also demonstrated in dogs with ventricular fibrillation induced by coronary occlusion; pretreatment with the compound (3.0 mg/kg i.v.) or glibenclamide (1.0 mg/kg i.v.) inhibited ventricular fibrillation and prevented reductions in refractory period, but glibenclamide, in contrast to HMR-1883, increased plasma levels of insulin and reduced blood glucose. In a study in rabbits subjected to ischemia–reperfusion, HMR-1883 (3 mg/kg i.v.) had no effect on myocardial infarct mass, whereas glibenclamide (0.3 mg/kg i.v.) produced a significant increase; however, title compound prevented the increase in left ventricular end-diastolic pressure (LVEDP). Another trial in rabbits showed that HMR-1883 did not abolish the cardioprotective effect of preconditioning, whereas glibenclamide totally reversed the effect of preconditioning.

SOURCE – Hoechst Marion Roussel.**REFERENCES**

1. Englert, H. et al. (Hoechst AG) *Substd. benzenesulfonylureas and -thioureas, process for their preparation and their use as pharmaceuticals*. CA 2116165, EP 612724, JP 95304728, US 5574069, US 5698596, US 5776980.

2. Billman, G.E. and Englert, H.C. *HMR 1883, a novel cardiosselective ATP-dependent potassium channel antagonist prevents ventricular fibrillation induced by myocardial ischemia*. Circulation 1997, 96(8, Suppl.): Abst 2780.

3. Gögelein, H. et al. *HMR 1883 - A novel KATP blocker with improved selectivity for heart muscle cells*. Naunyn-Schmied Arch Pharmacol 1998, 357(4, Suppl.): Abst 292.

4. Kelety, B. et al. *Effects of glibenclamide and HMR 1883 on KATP channels obtained by coexpression of human SUR1 and KIR6.2 in mammalian cells*. Naunyn-Schmied Arch Pharmacol 1998, 357(4, Suppl.): Abst 293.

5. Linz, W. et al. *Effect of KATP-channel blockade on myocardial infarct mass in anaesthetized rabbits*. Naunyn-Schmied Arch Pharmacol 1998, 357(4, Suppl.): Abst 295.

6. Linz, W. et al. *Different effects of KATP-channel blockers on ischemic preconditioning in anaesthetized rabbits*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 28.5.

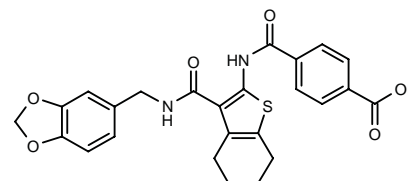
7. Wiemer, G. et al. *Effect of the new KATP-channel blocker HMR 1883 on reperfusion-induced ventricular fibrillation in isolated rat hearts*. Naunyn-Schmied Arch Pharmacol 1998, 357(4, Suppl.): Abst 294.

8. *Global research and development pipeline*. Hoechst Marion Roussel Product Pipeline 1997.

*Identified compound **218761** (see **214632**) Drug Data Rep 1995, 17(4): 343.

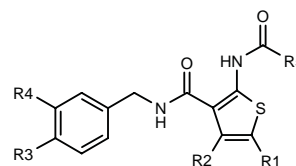
HEART FAILURE THERAPY**264843**

4-[*N*-[3-[*N*-(1,3-Benzodioxol-5-ylmethyl)carbamoyl]-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl]carbamoyl]-benzoic acid



C25-H22-N2-O6-S; Mol wt: 478.52

ACTION – An inhibitor of cyclic GMP phosphodiesterase (cGMP-PDE, PDE V) potentially useful for the treatment of cardiovascular disorders, particularly heart failure, and for impotence. Other specifically claimed compounds from this series of aminothiophene derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
265682	Me	H	H	H	4-CO2H-Ph	C ₂₁ H ₁₈ N ₂ O ₄ S
265683	Me	H	-OCH2O-		4-CO2H-Ph	C ₂₂ H ₁₈ N ₂ O ₆ S
265684	Me	H	-OCH2O-		4-CO2H-cyclohexyl	C ₂₂ H ₂₄ N ₂ O ₆ S
265686		-(CH2)4-	OMe	Cl	4-CO2H-Ph	C ₂₅ H ₂₃ ClN ₂ O ₅ S
265687	Me	H	OMe	Cl	4-CO2H-Ph	C ₂₂ H ₁₉ ClN ₂ O ₅ S
265688	Et	H	OMe	Cl	4-CO2H-Ph	C ₂₃ H ₂₁ ClN ₂ O ₅ S
265689		-(CH2)4-	OMe	Cl	4-CO2H-cyclohexyl	C ₂₅ H ₂₉ ClN ₂ O ₅ S
265690	Me	H	OMe	Cl	4-CO2H-cyclohexyl	C ₂₂ H ₂₅ ClN ₂ O ₅ S

SOURCE – Merck KGaA.

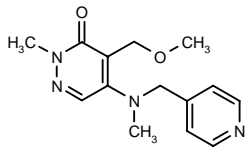
REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) *Aminothiophene carboxylic acid amides and the use thereof as phosphodiesterase inhibitors*. WO 9816521.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

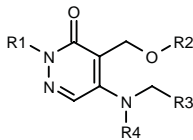
264998

4-(Methoxymethyl)-2-methyl-5-[N-methyl-N-(4-pyridylmethyl)amino]pyridazin-3(2H)-one



C14-H18-N4-O2; Mol wt: 274.32

ACTION – Agent for the treatment of shock states such as septic shock, hemorrhagic shock and cardiogenic shock, as well as multiple organ failure and ischemic diseases. Compound was found to be effective against lipopolysaccharide-induced mortality in rats (75% survival at 50 mg/kg i.p. vs. 0% in the control group) and PAF-induced motality in rats (92% inhibition at 12.5 mg/kg i.p.). Other specifically claimed compounds from this series of pyridazone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
265407	Me	H	4-Pyr	H	C ₁₂ H ₁₄ N ₄ O ₂
265408	t-Bu	H	4-Pyr	H	C ₁₅ H ₂₀ N ₄ O ₂
265409	Me	Me	3-Pyr	Me	C ₁₄ H ₁₈ N ₄ O ₂
265410	Me	Me	4-Pyr	H	C ₁₃ H ₁₆ N ₄ O ₂

SOURCE – Ishihara Sangyo.

REFERENCES

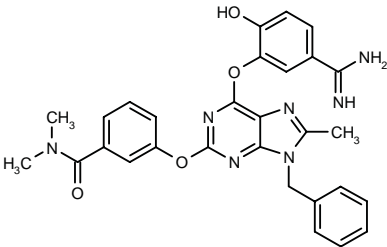
1. Shigehara, I. et al. (Ishihara Sangyo Co., Ltd.) *Pyridazinone derivs. or their salts, processes for their production, and anti-shock agents containing them*. US 5763439, WO 9507264.

AGENTS AFFECTING BLOOD
COAGULATION

ANTICOAGULANTS

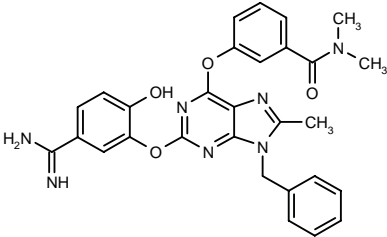
263306

3-[6-(5-Amidino-2-hydroxyphenoxy)-9-benzyl-8-methyl-purin-2-yloxy]-N,N-dimethylbenzamide



C29-H27-N7-O4; Mol wt: 537.58

ACTION – Anticoagulant that acts by inhibiting factor Xa. Another specifically claimed compound within this series of purine derivatives is:



265634: C29-H27-N7-O4

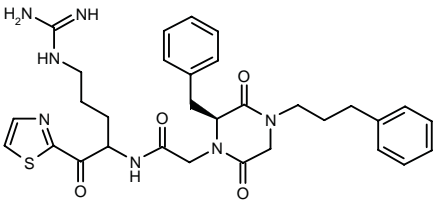
SOURCE – Schering AG.

REFERENCES

1. Morrissey, M.M. et al. (Schering AG) *Purine derivs. and their use as anti-coagulants*. US 5753635, WO 9807725.

263814

2-[2(S)-Benzyl-3,6-dioxo-4-(3-phenylpropyl)piperazin-1-yl]-N-[4-guanidino-1-(thiazol-2-ylcarbonyl)butyl]acetamide



C31-H37-N7-O4-S; Mol wt: 603.74

SOURCE – Merck KGaA.

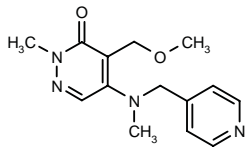
REFERENCES

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MISCELLANEOUS
CARDIOVASCULAR DRUGS

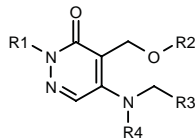
264998

4-(Methoxymethyl)-2-methyl-5-[N-methyl-N-(4-pyridylmethyl)amino]pyridazin-3(2H)-one



C14-H18-N4-O2; Mol wt: 274.32

ACTION – Agent for the treatment of shock states such as septic shock, hemorrhagic shock and cardiogenic shock, as well as multiple organ failure and ischemic diseases. Compound was found to be effective against lipopolysaccharide-induced mortality in rats (75% survival at 50 mg/kg i.p. vs. 0% in the control group) and PAF-induced motality in rats (92% inhibition at 12.5 mg/kg i.p.). Other specifically claimed compounds from this series of pyridazone derivatives include the following:



Compound	R1	R2	R3	R4	Formula
265407	Me	H	4-Pyr	H	C ₁₂ H ₁₄ N ₄ O ₂
265408	t-Bu	H	4-Pyr	H	C ₁₅ H ₂₀ N ₄ O ₂
265409	Me	Me	3-Pyr	Me	C ₁₄ H ₁₈ N ₄ O ₂
265410	Me	Me	4-Pyr	H	C ₁₃ H ₁₆ N ₄ O ₂

SOURCE – Ishihara Sangyo.

REFERENCES

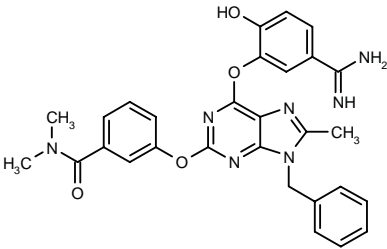
1. Shigehara, I. et al. (Ishihara Sangyo Co., Ltd.) *Pyridazinone derivs. or their salts, processes for their production, and anti-shock agents containing them*. US 5763439, WO 9507264.

AGENTS AFFECTING BLOOD
COAGULATION

ANTICOAGULANTS

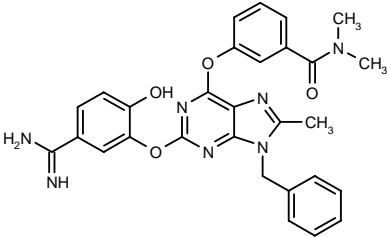
263306

3-[6-(5-Amidino-2-hydroxyphenoxy)-9-benzyl-8-methyl-purin-2-yloxy]-N,N-dimethylbenzamide



C29-H27-N7-O4; Mol wt: 537.58

ACTION – Anticoagulant that acts by inhibiting factor Xa. Another specifically claimed compound within this series of purine derivatives is:



265634: C29-H27-N7-O4

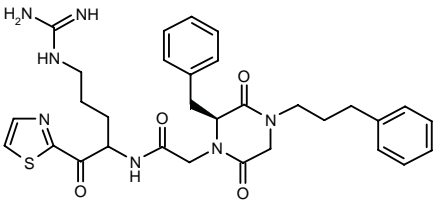
SOURCE – Schering AG.

REFERENCES

1. Morrissey, M.M. et al. (Schering AG) *Purine derivs. and their use as anti-coagulants*. US 5753635, WO 9807725.

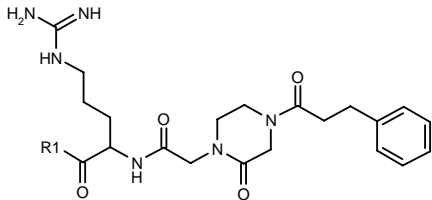
263814

2-[2(S)-Benzyl-3,6-dioxo-4-(3-phenylpropyl)piperazin-1-yl]-N-[4-guanidino-1-(thiazol-2-ylcarbonyl)butyl]acetamide



C31-H37-N7-O4-S; Mol wt: 603.74

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of human thrombin ($K_i = 10 \text{ nM}$) proven active in the FeCl_3 -induced carotid artery thrombosis model in rats and shown to prolong activated partial thromboplastin time (APTT) and thrombin time (TT) *in vitro*. Other compounds from this series of lactam derivatives include the following:



Compound	R1	Formula
265164	2-thiazolyl	$\text{C}_{24}\text{H}_{31}\text{N}_7\text{O}_4\text{S}$
265165	2-benzothiazolyl	$\text{C}_{28}\text{H}_{33}\text{N}_7\text{O}_4\text{S}$

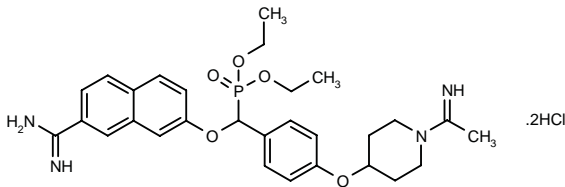
SOURCE – BioChem Pharma.

REFERENCES

1. St-Denis, Y. et al. (BioChem Pharma, Inc.) *Lactam inhibitors of thrombin*. WO 9809987.

264670

1-(7-Amidinonaphthalen-2-yloxy)-1-[4-[1-(1-iminoethyl)-piperidin-4-yloxy]phenyl]methylphosphonic acid diethyl ester dihydrochloride



C29-H37-N4-O5-P.2HCl; Mol wt: 625.53

ACTION – Anticoagulant, a potent and selective factor Xa inhibitor.

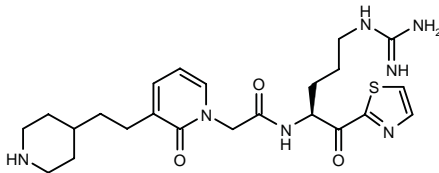
SOURCE – Boehringer Mannheim.

REFERENCES

1. Kucznierz, R. et al. (Boehringer Mannheim GmbH) *Novel phosphonates, process for their preparation and pharmaceutical compsns*. EP 842941, WO 9822483.

264844

2-[N^α -[2-[2-Oxo-3-[2-(4-piperidiny)ethyl]-1,2-dihydropyridin-1-yl]acetyl]-L-arginyl]thiazole



C23-H33-N7-O3-S; Mol wt: 487.62

ACTION – Anticoagulant, a highly selective inhibitor of factor Xa.

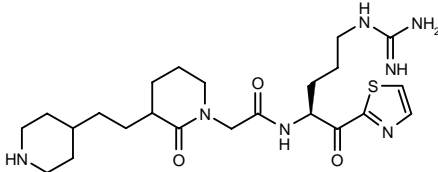
SOURCE – Cor Therapeutics.

REFERENCES

1. Zhu, B.-Y. and Scarborough, R.M. (Cor Therapeut., Inc.) *Heterocyclic derivs. as factor Xa inhibitors*. WO 9816524.

264845

2-[N^α -[2-[2-Oxo-3-[2-(4-piperidiny)ethyl]piperidin-1-yl]-acetyl]-L-arginyl]thiazole



C23-H37-N7-O3-S; 491.65

ACTION – Anticoagulant, a selective inhibitor of factor Xa.

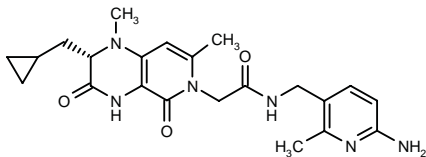
SOURCE – Cor Therapeutics.

REFERENCES

1. Zhu, B.-Y. and Scarborough, R.M. (Cor Therapeut., Inc.) *Selective factor Xa inhibitors*. WO 9816525.

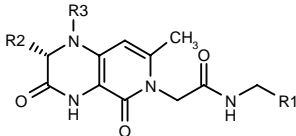
264863

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[2(*S*)-(cyclopropylmethyl)-1,7-dimethyl-3,5-dioxo-1,2,3,4,5,6-hexahydropyrido[3,4-*b*]pyrazin-6-yl]acetamide



C22-H28-N6-O3; Mol wt: 424.50

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human thrombin ($K_i < 1.0 \text{ nM}$). Other specifically claimed compounds from this series of bicyclic pyridones include the following:



Compound	R1	R2	R3	Formula
265784	6-NH2-2-Me-3-Pyr	cyclopropyl-CH2	H	$\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_3$
265785	2-(cyclopropyl-NH-COCH2O)-5-Cl-Ph	CH2Ph	H	$\text{C}_{29}\text{H}_{30}\text{ClN}_5\text{O}_5$
265786	6-NH2-2-Me-3-Pyr	CH2Ph	H	$\text{C}_{24}\text{H}_{26}\text{N}_6\text{O}_3$
265787	6-NH2-2-Me-3-Pyr	-(CH2)4-		$\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_3$
265788	6-NH2-2-Me-3-Pyr	H	CH2Ph	$\text{C}_{24}\text{H}_{26}\text{N}_6\text{O}_3$
265789	6-NH2-3-Pyr	cyclopropyl-CH2	Me	$\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_3$
265790	2-(cyclopropyl-NH-COCH2O)-Ph	cyclopropyl-CH2	Me	$\text{C}_{27}\text{H}_{33}\text{N}_5\text{O}_5$

SOURCE – Merck & Co.

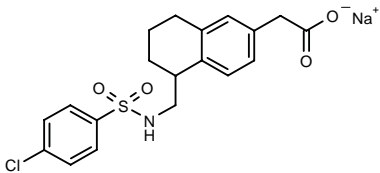
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ANTIPLATELET THERAPY

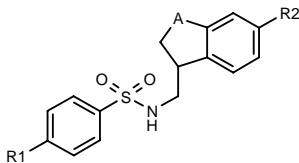
264328

2-[5-(4-Chlorophenylsulfonamidomethyl)-5,6,7,8-tetrahydro-2-naphthyl]acetic acid sodium salt

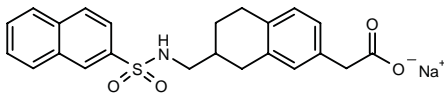


C19-H19-Cl-N-Na-O4-S; Mol wt: 415.87

ACTION – Potent Tx_A₂ antagonist shown to inhibit U-46619-induced aggregation of guinea pig platelet-rich plasma (PRP) with a pIC₅₀ value of 6.73. No mortality was observed following administration of 300 mg/kg p.o. to mice. Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	R2	A	Formula
265546	Br	CH2COO ⁻ Na ⁺	-(CH2)2-	C ₁₉ H ₁₉ BrNNaO ₄ S
265548	Br	CH2COO ⁻ Na ⁺	-CH2-	C ₁₈ H ₁₇ BrNNaO ₄ S
265549	Cl	OCH2COO ⁻ Na ⁺	-CH2-	C ₁₈ H ₁₇ ClNNaO ₅ S



265545: C23-H22-N-Na-O4-S

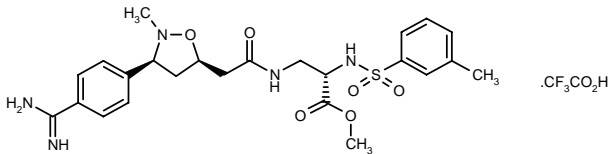
SOURCE – Zeria.

REFERENCES

1. Shinozaki, K. et al. (Zeria Pharm. Co., Ltd.) *Sulfonamide derivs., thromboxane antagonists containing them and their intermediates*. JP 98087602.

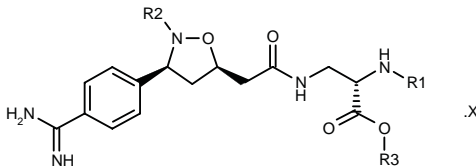
263255

cis-3-[2-[3-(4-Amidinophenyl)-2-methylisoxazolidin-5-yl]acetamido]-2(*S*)-(3-methylphenylsulfonamido)propionic acid methyl ester trifluoroacetate

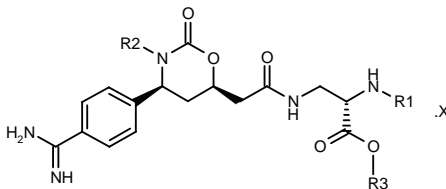


C24-H31-N5-O6-S.C2-H-F3-O2; Mol wt: 631.62

ACTION – Platelet aggregation inhibitor and anti-thrombotic agent, a fibrinogen (gpIIb/IIIa) receptor antagonist. Within this series of specifically claimed cyclic carbamates and isoxazolidines, the following are also included:



Compound	R1	R2	R3	X	Formula
263768	3-Me-PhSO2	CH2Ph	Me	CF3CO2H	C ₃₀ H ₃₅ N ₅ O ₆ S .C ₂ HF ₃ O ₂
263769	3-Me-PhSO2	i-Pr	H	HCl	C ₂₅ H ₃₃ N ₅ O ₆ S.HCl
263770	3,5-(Me)2- -4-isoxazolyl-SO2	Me	Me	CF3CO2H	C ₂₂ H ₃₀ N ₆ O ₇ S .C ₂ HF ₃ O ₂
263771	CO2Bu	Me	Me	CF3CO2H	C ₂₂ H ₃₃ N ₅ O ₆ .C ₂ HF ₃ O ₂
263772	3-Me-PhSO2	Ph	H	HCl	C ₂₈ H ₃₁ N ₅ O ₆ S.HCl



Compound	R1	R2	R3	R4	Formula
263773	3-Me-PhSO2	Me	Me	CF3CO2H	C ₂₅ H ₃₁ N ₅ O ₇ S .C ₂ HF ₃ O ₂
263774	3-Me-PhSO2	CH2Ph	H	HCl	C ₃₀ H ₃₃ N ₅ O ₇ S.HCl
263775	3,5-(Me)2- -4-isoxazolyl-SO2	Me	Me	CF3CO2H	C ₂₃ H ₃₀ N ₆ O ₈ S .C ₂ HF ₃ O ₂
263776	CO2Bu	Me	H	HCl	C ₂₂ H ₃₁ N ₅ O ₇ .HCl

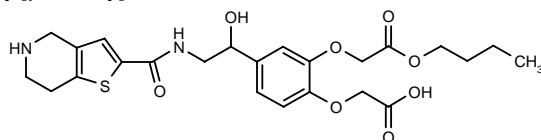
SOURCE – DuPont Merck (now DuPont Pharm.).

REFERENCES

1. Jin, F. and Confalone, P.N. (The Du Pont Merck Pharm. Co.) *Cyclic carbamates and isoxazolidines as IIb/IIIa antagonists*. WO 9806707.

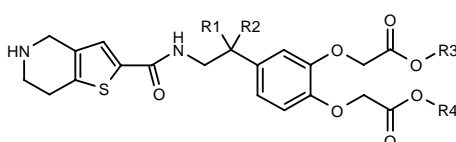
264358

2-[2-(Butoxycarbonylmethoxy)-4-[1-hydroxy-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-ylcarboxamido)-ethyl]phenoxy]acetic acid



C24-H30-N2-O8-S; Mol wt: 506.57

ACTION – Platelet aggregation inhibitor that exhibits an IC_{50} value of 0.28 μ M for inhibition of ADP-induced aggregation of human platelet-rich plasma (PRP). A representative compound from a series of acetic acid derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
265565		-O-	Bu	H	C ₂₄ H ₂₈ N ₂ O ₈ S
265566		-O-	H	Bu	C ₂₄ H ₂₈ N ₂ O ₈ S
265567	H	OH	H	Bu	C ₂₄ H ₃₀ N ₂ O ₈ S

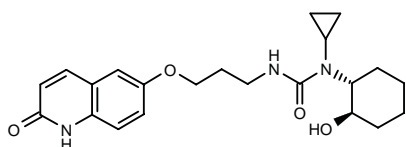
SOURCE – Meiji Seika.

REFERENCES

1. Ohta, K. et al. (Meiji Seika Kaisha, Ltd.) *Carboxylic acid derivs. having platelet aggregation inhibitory effect*. JP 98101677.

OPC-33509***255831**

(-)-(R,R)-N-Cyclopropyl-N-(2-hydroxycyclohexyl)-N'-[3-(2-oxo-1,2-dihydroquinolin-6-yloxy)propyl]urea



C22-H29-N3-O4; Mol wt: 399.49

ACTION – Antithrombotic and antihyperplastic agent selected for further development as a candidate for the treatment of ischemic diseases. It demonstrated potent *in vitro* activity as an inhibitor of phosphodiesterase type III (PDE III) and platelet aggregation induced by collagen and ADP (IC_{50} = 2.2 and 2.3 μ M, respectively, in rabbit platelets). It was significantly more active than cilostazol after oral administration in the collagen-induced mouse pulmonary thromboembolism model (ED_{50} = 2 mg/kg p.o. vs. 12 mg/kg p.o. for cilostazol), and it was also effective in a rat model of peripheral circulatory insufficiency induced by sodium laurate, providing significant inhibition against ulcer development at oral doses of 10 and 30 mg/kg. Compound inhibited intimal thickening in a rat carotid artery balloon injury model of restenosis.

SOURCE – Otsuka.

REFERENCES

1. Koga, Y. et al. (Otsuka Pharm. Co., Ltd.) *Carbostyryl derivs*. JP 97157258.
2. Inoue, Y. et al. *A new antithrombotic agent OPC-33509 - Inhibitory effects on experimental thrombosis and hyperplasia*. Thromb Haemost 1997, Suppl.: Abst PS-2825.
3. Inoue, Y. et al. *Novel antithrombotic agent, OPC-33509 - Inhibitory effect to vascular stenosis*. Jpn J Thromb Hemostasis 1997, 8(4): Abst 88.
4. Inoue, Y. et al. *A new anti-thrombotic agent OPC-33509 - Inhibitory effects on experimental thrombosis and vascular intimal thickening*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-323.
5. Koga, Y. et al. *2(1H)-Quinolone derivatives as novel anti-arteriosclerotic agents showing anti-thrombotic and anti-hyperplastic activities*. Bioorg Med Chem Lett 1998, 8(12): 1471.

*Identified compound **255831** (see **253614**) Drug Data Rep 1997, 19(11): 996.

THROMBOLYTICS**MONTEPLASE**

Rec INN

171004

Modified human tissue plasminogen activator in which cysteine 84 in the epidermal growth factor domain is replaced by serine

84-L-Serineplasminogen activator (human tissue-type 2-chain form), cyclic (6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→264), (134'→ 209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadecakis(disulfide)

E-6010⁺

Mf-tPA

ACTION – Thrombolytic agent, a modified human tissue plasminogen activator obtained using recombinant DNA technology with an extended half-life.

INDICATION – Treatment of acute myocardial infarction.

PRESENTATION – Vials for bolus injection, 400, 800 and 1600 IU.

PROPRIETARY NAME – Cleactor (JP).

SOURCE – Eisai.

RECENT REFERENCES

1. Matsubara, T. et al. *Comparative study of intravenous thrombolytic therapy with second generation recombinant tPA (E6010) and myocardial salvage effect of primary PTCA: Quantitative evaluation of ^{99m}Tc-MIBI*. Jpn Circ J 1995, 59(Suppl. 1): Abst 0538.
2. Mizuo, H. et al. *Studies on the metabolic fate of modified recombinant tissue-type plasminogen activator (E6010) (2): Blood or plasma concentration, distribution, metabolism and excretion in rats after repeated intravenous administration of ¹²⁵I-E6010*. Xenobiotic Metab Dispos 1996, 11(6): 585.
3. Mizuo, H. et al. *Studies on the metabolic fate of modified recombinant tissue-type plasminogen activator (E6010) (3): Feto-placental transfer and excretion into milk in rats after a single intravenous administration of ¹²⁵I-E6010*. Xenobiotic Metab Dispos 1996, 11(6): 599.
4. Mizuo, H. et al. *Studies on the metabolic fate of modified recombinant tissue-type plasminogen activator (E6010) (1): Blood or plasma concentration, distribution, metabolism and excretion in rats after a single intravenous administration of ¹²⁵I-E6010 in comparison with ¹²⁵I-recombinant tissue-type plasminogen activator (rt-PA)*. Xenobiotic Metab Dispos 1996, 11(6): 556.

5. Saito, M. et al. *A novel modified tissue-type plasminogen activator (t-PA), E6010, reduces reperfusion arrhythmias induced after coronary thrombolysis: Comparison of native t-PA and urokinase.* Jpn Circ J 1995, 59(8): 556.

6. Suzuki, S. et al. *A novel modified t-PA, E-6010, induces faster recovery of ventricular function after coronary thrombolysis than native t-PA in a canine thrombosis model.* Jpn Circ J 1995, 59(4): 205.

7. Suzuki, S. et al. *A novel modified t-PA, E-6010, induces faster recovery of ventricular function after coronary thrombolysis than native t-PA in a canine thrombosis model.* (Erratum). Jpn Circ J 1995, 59(8): 587.

8. Suzuki, S. et al. *Thrombolytic properties of a novel modified t-PA, E6010, in a canine model with copper coil-induced coronary artery thrombi: Comparison with tistreptase.* Jpn Pharmacol Ther 1996, 24(6): 97.

9. *Eisai launches monteplase in first market.* Prous Science Daily Essentials June 16, 1998.

10. *Eisai launches myocardial infarction treatment Cleactor®.* Eisai Co., Ltd. Press Release 1998, June 15.

11. *Monteplase launch.* Eisai Co., Ltd. Company Communication 1998, June 16.

*Drug Data Rep 1991, 13(7): 585.

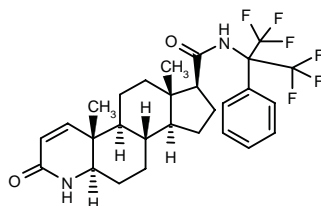
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

PNU-157706*

250078

3-Oxo-N-[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl]-4-aza-5 α -androst-1-ene-17 β -carboxamide



C28-H32-F6-N2-O2; Mol wt: 542.56

ACTION – Agent for the treatment of benign prostatic hyperplasia, a dual inhibitor of type I and type II 5 α -reductase (IC₅₀ = 20 and 34 nM, respectively, against human and rat prostatic enzyme; IC₅₀ = 3.9 and 1.8 nM, respectively, against recombinant human type I and type II enzyme), with little or no binding affinity for rat prostate androgen receptors (IC₅₀ = 20 μ M; relative binding affinity [RBA] = 0.009% that of dihydrotestosterone). *In vivo*, a single oral dose of 10 mg/kg in adult rats reduced prostatic DHT concentrations by 74% at 6 h and 89% at 24 h (vs. 80 and 47%, respectively, for finasteride), and increased prostatic testosterone levels. It significantly reduced ventral prostate and seminal vesicle growth in testosterone-implanted prepubertal castrated rats treated with 10 mg/kg/day p.o. for 7 days, and in adult rats (ED₅₀ = 0.12 and 0.13 mg/kg/day x 28 days).

SOURCE – Pharmacia & Upjohn.

REFERENCES

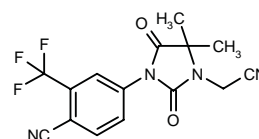
1. Panzeri, A. et al. (Pharmacia SpA) *Phenylsubstd. 4-azasteroid fluoroderivs.* EP 793671, WO 9710257.
2. di Salle, E. et al. *PNU 157706, a novel dual type I and II 5 α -reductase inhibitor.* J Steroid Biochem Molec Biol 1998, 64(3-4): 179.

*Identified compound **250078** Drug Data Rep 1997, 19(7): 628.

RU-58642

263481

2-[3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxo-1-imidazolidinyl]acetonitrile



C15-H11-F3-N4-O2; Mol wt: 336.27

ACTION – Agent for the treatment of androgen-dependent disorders including benign prostatic hypertrophy and prostate cancer, a potent androgen receptor antagonist (relative binding affinity [RBA] using rat prostate receptors = 46% that of testosterone) with high selectivity relative to other steroid receptors. *In vitro*, compound inhibited the dihydrotestosterone-induced chloramphenicol acetyl transferase (CAT) activity in breast cancer T47D cells with an IC₅₀ of 1 nM. It produced a significant decrease in prostate and seminal vesicle weight in testosterone-treated castrated rats following either s.c. or p.o. administration at a dose of 0.3 mg/kg (53 and 55% inhibition of the increase in prostate weight, respectively), and also in intact rats after 0.3 mg/kg s.c. or 1 mg/kg p.o.

SOURCE – Hoechst Marion Roussel.

REFERENCES

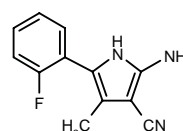
1. Gaillard-Kelly, M. et al. (Roussel-Uclaf) *Phenylimidazolidines, their process for fabrication, their application as medicaments and the pharmaceutical compns. containing them.* EP 494819, FR 2671348, JP 92308579, US 5411981.
2. Battmann, T. et al. *Pharmacological profile of RU 58642, a potent systemic antiandrogen for the treatment of androgen-dependent disorders.* J Steroid Biochem Mol Biol 1998, 64(1-2): 103.

TREATMENT OF URINARY INCONTINENCE

NS-8*

246700

2-Amino-5-(2-fluorophenyl)-4-methyl-1H-pyrrole-3-carbonitrile



C12-H10-F-N3; Mol wt: 215.23

5. Saito, M. et al. *A novel modified tissue-type plasminogen activator (t-PA), E6010, reduces reperfusion arrhythmias induced after coronary thrombolysis: Comparison of native t-PA and urokinase.* Jpn Circ J 1995, 59(8): 556.

6. Suzuki, S. et al. *A novel modified t-PA, E-6010, induces faster recovery of ventricular function after coronary thrombolysis than native t-PA in a canine thrombosis model.* Jpn Circ J 1995, 59(4): 205.

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*Drug Data Rep 1991, 13(7): 585.

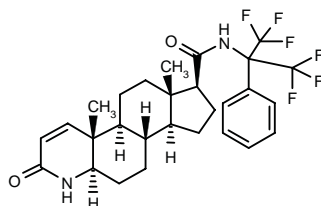
RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

PNU-157706*

250078

3-Oxo-N-[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl]-4-aza-5 α -androst-1-ene-17 β -carboxamide



C28-H32-F6-N2-O2; Mol wt: 542.56

ACTION – Agent for the treatment of benign prostatic hyperplasia, a dual inhibitor of type I and type II 5 α -reductase (IC₅₀ = 20 and 34 nM, respectively, against human and rat prostatic enzyme; IC₅₀ = 3.9 and 1.8 nM, respectively, against recombinant human type I and type II enzyme), with little or no binding affinity for rat prostate androgen receptors (IC₅₀ = 20 μ M; relative binding affinity [RBA] = 0.009% that of dihydrotestosterone). *In vivo*, a single oral dose of 10 mg/kg in adult rats reduced prostatic DHT concentrations by 74% at 6 h and 89% at 24 h (vs. 80 and 47%, respectively, for finasteride), and increased prostatic testosterone levels. It significantly reduced ventral prostate and seminal vesicle growth in testosterone-implanted prepubertal castrated rats treated with 10 mg/kg/day p.o. for 7 days, and in adult rats (ED₅₀ = 0.12 and 0.13 mg/kg/day x 28 days).

SOURCE – Pharmacia & Upjohn.

REFERENCES

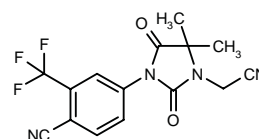
1. Panzeri, A. et al. (Pharmacia SpA) *Phenylsubst. 4-azasteroid fluoroderivs.* EP 793671, WO 9710257.
2. di Salle, E. et al. *PNU 157706, a novel dual type I and II 5 α -reductase inhibitor.* J Steroid Biochem Molec Biol 1998, 64(3-4): 179.

*Identified compound **250078** Drug Data Rep 1997, 19(7): 628.

RU-58642

263481

2-[3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxo-1-imidazolidinyl]acetonitrile



C15-H11-F3-N4-O2; Mol wt: 336.27

ACTION – Agent for the treatment of androgen-dependent disorders including benign prostatic hypertrophy and prostate cancer, a potent androgen receptor antagonist (relative binding affinity [RBA] using rat prostate receptors = 46% that of testosterone) with high selectivity relative to other steroid receptors. *In vitro*, compound inhibited the dihydrotestosterone-induced chloramphenicol acetyl transferase (CAT) activity in breast cancer T47D cells with an IC₅₀ of 1 nM. It produced a significant decrease in prostate and seminal vesicle weight in testosterone-treated castrated rats following either s.c. or p.o. administration at a dose of 0.3 mg/kg (53 and 55% inhibition of the increase in prostate weight, respectively), and also in intact rats after 0.3 mg/kg s.c. or 1 mg/kg p.o.

SOURCE – Hoechst Marion Roussel.

REFERENCES

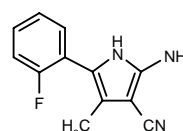
1. Gaillard-Kelly, M. et al. (Roussel-Uclaf) *Phenylimidazolidines, their process for fabrication, their application as medicaments and the pharmaceutical compns. containing them.* EP 494819, FR 2671348, JP 92308579, US 5411981.
2. Battmann, T. et al. *Pharmacological profile of RU 58642, a potent systemic antiandrogen for the treatment of androgen-dependent disorders.* J Steroid Biochem Mol Biol 1998, 64(1-2): 103.

TREATMENT OF URINARY INCONTINENCE

NS-8*

246700

2-Amino-5-(2-fluorophenyl)-4-methyl-1H-pyrrole-3-carbonitrile



C12-H10-F-N3; Mol wt: 215.23

ACTION – Agent for the treatment of urinary incontinence, a detrusor-selective Ca²⁺-sensitive potassium channel opener that suppresses the micturition reflex by inhibiting the activity of the afferent pelvic nerve.

SOURCE – Nippon Shinyaku.

REFERENCES

1. Tsuda, M. et al. (Nippon Shinyaku Co., Ltd.) *Pyrrole derivs. and medicinal compsn.* WO 9640634.

2. Tanaka, M. et al. *A novel pyrrole derivative, NS-8, activates the Ca2+-sensitive K+-channels and suppresses micturition reflex in rats.* J Urol 1998, 159(5, Suppl.): Abst 81.

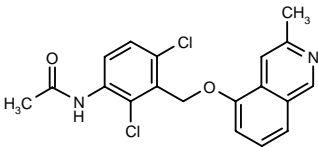
*Identified compound **246700** Drug Data Rep 1997, 19(5): 431.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

264329

N-[2,4-Dichloro-3-(3-methylisoquinolin-5-yloxymethyl)-phenyl]acetamide



C19-H16-Cl2-N2-O2; Mol wt: 375.25

ACTION – Antimicrobial agent active against *Helicobacter pylori* (MIC < 0.02 µg/ml against *H. pylori* FP 1757).

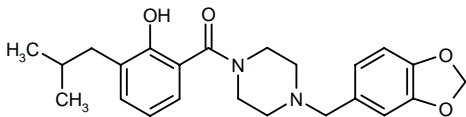
SOURCE – Fujisawa.

REFERENCES

1. David, V. et al. (Fujisawa Pharm. Co., Ltd.) *Novel isoquinoline derivs. and their medicinal use.* JP 98087629.

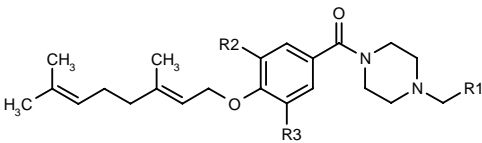
264661

1-(1,3-Benzodioxol-5-ylmethyl)-4-(2-hydroxy-3-isobutyl-benzoyl)piperazine

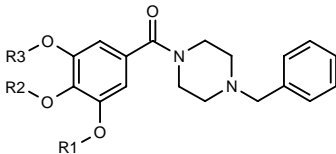


C23-H28-N2-O4; Mol wt: 396.49

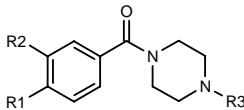
ACTION – Antiulcer agent active against *Helicobacter pylori* (MIC < 3.13 µg/ml), found to produce 93.1% inhibition of gastric acid secretion in isolated rabbit gastric fundus gland suspensions at a concentration of 10 µM. It also shows a good safety profile. Within this series of *N*-acylpiperazine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
264810	1,3-benzodioxol-5-yl- -CONHCH2	H	H	C ₃₁ H ₃₉ N ₃ O ₅
264811	1,3-benzodioxol-5-yl- -CONHCH2	H	i-Bu	C ₃₅ H ₄₇ N ₃ O ₅
264812	4-Pyr-COOCH2	H	H	C ₂₉ H ₃₇ N ₃ O ₄
264813	1,3-benzodioxol-5-yl	H	H	C ₂₉ H ₃₆ N ₂ O ₄
264814	Ph	OMe	OMe	C ₃₀ H ₄₀ N ₂ O ₄



Compound	R1	R2=R3	Formula
264815	CH2CH=C(Me)2	CH2CH=C(Me)2	C ₃₃ H ₄₄ N ₂ O ₄
264816	(E)-CH2CH=C(Me)- CH2CH2CH=C(Me)2	Me	C ₃₀ H ₄₀ N ₂ O ₄



Compound	R1	R2	R3	Formula
264817	4-F-PhCH2O	i-Bu	i-PrNHCO	C ₂₆ H ₃₄ FN ₃ O ₃
264818	OCH2Ph	i-Bu	CH2Ph	C ₂₉ H ₃₄ N ₂ O ₂
264819	4-F-PhCH2O	i-Bu	2-Pyr	C ₂₇ H ₃₀ FN ₃ O ₂
264820	i-Bu	OH	CH(Ph)2	C ₂₈ H ₃₂ N ₂ O ₂

SOURCE – Shiseido.

REFERENCES

1. Nishino, C. et al. (Shiseido Co., Ltd.) *N-Acylpiperazine deriv., anti-ulcer drug, and antibacterial drug.* EP 832887, JP 98152487.

ENDOCRINE DRUGS

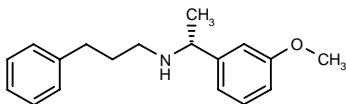
THYROID DISEASE THERAPY

NPS-467

264065

N-[1(*R*)-(3-Methoxyphenyl)ethyl]-3-phenyl-1-propanamine

NPS-R-467



C18-H23-N-O; Mol wt: 269.39

ACTION – Agent for the treatment of urinary incontinence, a detrusor-selective Ca²⁺-sensitive potassium channel opener that suppresses the micturition reflex by inhibiting the activity of the afferent pelvic nerve.

SOURCE – Nippon Shinyaku.

REFERENCES

1. Tsuda, M. et al. (Nippon Shinyaku Co., Ltd.) *Pyrrole derivs. and medicinal compsn.* WO 9640634.

2. Tanaka, M. et al. *A novel pyrrole derivative, NS-8, activates the Ca2+-sensitive K+-channels and suppresses micturition reflex in rats.* J Urol 1998, 159(5, Suppl.): Abst 81.

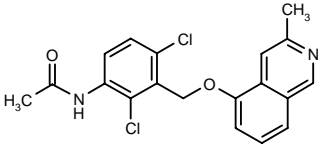
*Identified compound **246700** Drug Data Rep 1997, 19(5): 431.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

264329

N-[2,4-Dichloro-3-(3-methylisoquinolin-5-yloxymethyl)-phenyl]acetamide



C19-H16-Cl2-N2-O2; Mol wt: 375.25

ACTION – Antimicrobial agent active against *Helicobacter pylori* (MIC < 0.02 µg/ml against *H. pylori* FP 1757).

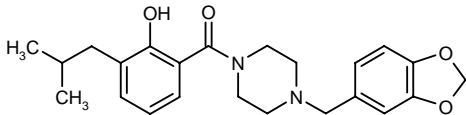
SOURCE – Fujisawa.

REFERENCES

1. David, V. et al. (Fujisawa Pharm. Co., Ltd.) *Novel isoquinoline derivs. and their medicinal use.* JP 98087629.

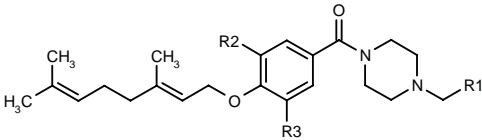
264661

1-(1,3-Benzodioxol-5-ylmethyl)-4-(2-hydroxy-3-isobutyl-benzoyl)piperazine

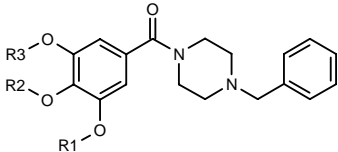


C23-H28-N2-O4; Mol wt: 396.49

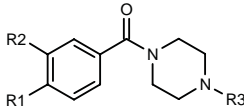
ACTION – Antiulcer agent active against *Helicobacter pylori* (MIC < 3.13 µg/ml), found to produce 93.1% inhibition of gastric acid secretion in isolated rabbit gastric fundus gland suspensions at a concentration of 10 µM. It also shows a good safety profile. Within this series of *N*-acylpiperazine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
264810	1,3-benzodioxol-5-yl- -CONHCH2	H	H	C ₃₁ H ₃₉ N ₃ O ₅
264811	1,3-benzodioxol-5-yl- -CONHCH2	H	i-Bu	C ₃₅ H ₄₇ N ₃ O ₅
264812	4-Pyr-COOCH2	H	H	C ₂₉ H ₃₇ N ₃ O ₄
264813	1,3-benzodioxol-5-yl	H	H	C ₂₉ H ₃₆ N ₂ O ₄
264814	Ph	OMe	OMe	C ₃₀ H ₄₀ N ₂ O ₄



Compound	R1	R2=R3	Formula
264815	CH2CH=C(Me)2	CH2CH=C(Me)2	C ₃₃ H ₄₄ N ₂ O ₄
264816	(E)-CH2CH=C(Me)- CH2CH2CH=C(Me)2	Me	C ₃₀ H ₄₀ N ₂ O ₄



Compound	R1	R2	R3	Formula
264817	4-F-PhCH2O	i-Bu	i-PrNHCO	C ₂₆ H ₃₄ FN ₃ O ₃
264818	OCH2Ph	i-Bu	CH2Ph	C ₂₉ H ₃₄ N ₂ O ₂
264819	4-F-PhCH2O	i-Bu	2-Pyr	C ₂₇ H ₃₀ FN ₃ O ₂
264820	i-Bu	OH	CH(Ph)2	C ₂₈ H ₃₂ N ₂ O ₂

SOURCE – Shiseido.

REFERENCES

1. Nishino, C. et al. (Shiseido Co., Ltd.) *N-Acylpiperazine deriv., anti-ulcer drug, and antibacterial drug.* EP 832887, JP 98152487.

ENDOCRINE DRUGS

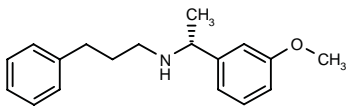
THYROID DISEASE THERAPY

NPS-467

264065

N-[1(R)-(3-Methoxyphenyl)ethyl]-3-phenyl-1-propanamine

NPS-R-467



C18-H23-N-O; Mol wt: 269.39

ACTION – Agent for the treatment of urinary incontinence, a detrusor-selective Ca²⁺-sensitive potassium channel opener that suppresses the micturition reflex by inhibiting the activity of the afferent pelvic nerve.

SOURCE – Nippon Shinyaku.

REFERENCES

1. Tsuda, M. et al. (Nippon Shinyaku Co., Ltd.) *Pyrrole derivs. and medicinal compsn.* WO 9640634.

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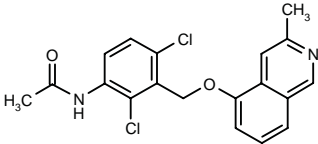
*Identified compound **246700** Drug Data Rep 1997, 19(5): 431.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

264329

N-[2,4-Dichloro-3-(3-methylisoquinolin-5-yloxymethyl)-phenyl]acetamide



C19-H16-Cl2-N2-O2; Mol wt: 375.25

ACTION – Antimicrobial agent active against *Helicobacter pylori* (MIC < 0.02 µg/ml against *H. pylori* FP 1757).

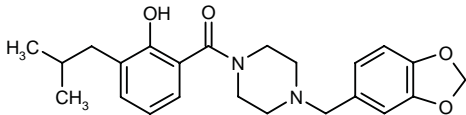
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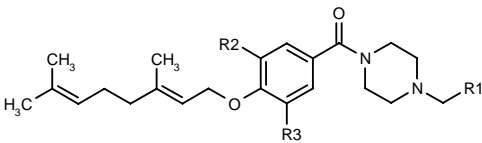
264661

1-(1,3-Benzodioxol-5-ylmethyl)-4-(2-hydroxy-3-isobutyl-benzoyl)piperazine

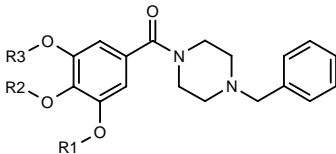


C23-H28-N2-O4; Mol wt: 396.49

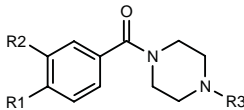
ACTION – Antiulcer agent active against *Helicobacter pylori* (MIC < 3.13 µg/ml), found to produce 93.1% inhibition of gastric acid secretion in isolated rabbit gastric fundus gland suspensions at a concentration of 10 µM. It also shows a good safety profile. Within this series of *N*-acylpiperazine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
264810	1,3-benzodioxol-5-yl- -CONHCH2	H	H	C ₃₁ H ₃₉ N ₃ O ₅
264811	1,3-benzodioxol-5-yl- -CONHCH2	H	i-Bu	C ₃₅ H ₄₇ N ₃ O ₅
264812	4-Pyr-COOCH2	H	H	C ₂₉ H ₃₇ N ₃ O ₄
264813	1,3-benzodioxol-5-yl	H	H	C ₂₉ H ₃₆ N ₂ O ₄
264814	Ph	OMe	OMe	C ₃₀ H ₄₀ N ₂ O ₄



Compound	R1	R2=R3	Formula
264815	CH2CH=C(Me)2	CH2CH=C(Me)2	C ₃₃ H ₄₄ N ₂ O ₄
264816	(E)-CH2CH=C(Me)- CH2CH2CH=C(Me)2	Me	C ₃₀ H ₄₀ N ₂ O ₄



Compound	R1	R2	R3	Formula
264817	4-F-PhCH2O	i-Bu	i-PrNHCO	C ₂₆ H ₃₄ FN ₃ O ₃
264818	OCH2Ph	i-Bu	CH2Ph	C ₂₉ H ₃₄ N ₂ O ₂
264819	4-F-PhCH2O	i-Bu	2-Pyr	C ₂₇ H ₃₀ FN ₃ O ₂
264820	i-Bu	OH	CH(Ph)2	C ₂₈ H ₃₂ N ₂ O ₂

SOURCE – Shiseido.

REFERENCES

1. Nishino, C. et al. (Shiseido Co., Ltd.) *N-Acylpiperazine deriv., anti-ulcer drug, and antibacterial drug.* EP 832887, JP 98152487.

ENDOCRINE DRUGS

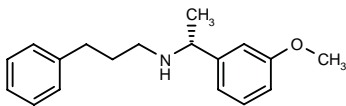
THYROID DISEASE THERAPY

NPS-467

264065

N-[1(R)-(3-Methoxyphenyl)ethyl]-3-phenyl-1-propanamine

NPS-R-467



C18-H23-N-O; Mol wt: 269.39

ACTION – Calcimimetic, a potent and selective positive allosteric modulator of the parathyroid cell Ca^{2+} receptor. It inhibited parathyroid hormone (PTH) secretion (10 nM and above) and increased cytoplasmic Ca^{2+} concentrations in bovine parathyroid cells in the presence of extracellular Ca^{2+} ; similar results were obtained using HEK 293 cells expressing the human parathyroid cell Ca^{2+} receptor. Title compound did not affect the responses to a variety of other G-protein-coupled receptors. Potentially useful for the treatment of primary and also secondary hyperparathyroidism.

SOURCE – NPS Pharm.

REFERENCES

1. Nemeth, E.F. et al. (NPS Pharm., Inc.) *Calcium receptor active molecules*. WO 9304373.

2. Bukoski, R.D. and Bian, K. (Univ. Texas System) *Methods of identifying modulators of perivascular sensory nerve Ca^{2+} receptors*. WO 9742951.

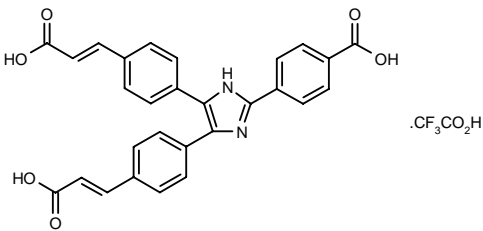
3. Cima, R.R. et al. *Identification and functional assay of an extracellular calcium-sensing receptor in *Necturus gastric mucosa**. Amer J Physiol 1997, 273(5, Part 1): G1051.

4. Nemeth, E.F. et al. *Calcimimetics with potent and selective activity on the parathyroid calcium receptor*. Proc Natl Acad Sci USA 1998, 95(7): 4040.

ANTIDIABETIC DRUGS

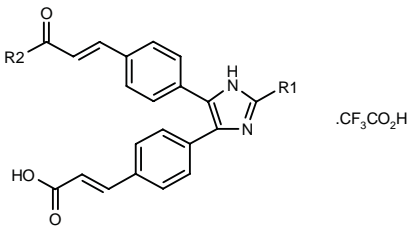
263745

4-[4,5-Bis[4-[2(*E*)-carboxyvinyl]phenyl]-1*H*-imidazol-2-yl]benzoic acid trifluoroacetate



C28-H20-N2-O6.C2-H-F3-O2; Mol wt: 594.50

ACTION – An inhibitor of protein tyrosine phosphatases (PTPases) such as PTP1B (IC_{50} = 0.072 μM) and CD45 (IC_{50} = 0.73 μM), claimed for the treatment of a broad range of conditions including diabetes, insulin resistance, obesity, immune dysfunction, autoimmune disorders, AIDS, osteoporosis, cancer, psoriasis, Alzheimer's disease and schizophrenia. Other related compounds include the following:



Compound	R1	R2	Formula
264099	H	OH	C ₂₁ H ₁₆ N ₂ O ₄ .C ₂ HF ₃ O ₂
264100	2-NO2-3-MeO-Ph	NH(CH2)4Ph	C ₃₆ H ₃₄ N ₄ O ₆ .C ₂ HF ₃ O ₂
264101	2-Me-5-MeO-Ph	NHPr	C ₃₂ H ₃₁ N ₃ O ₄ .C ₂ HF ₃ O ₂

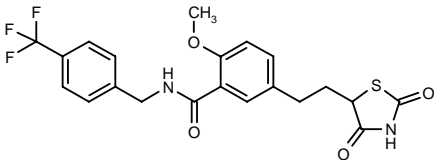
SOURCE – Ontogen.

REFERENCES

1. Mjalli, A. et al. (Ontogen Corp.) *Modulators of proteins with phosphotyrosine recognition units*. US 5753687, US 5770620.

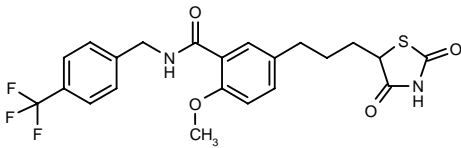
264330

5-[2-(2,4-Dioxothiazolidin-5-yl)ethyl]-2-methoxy-*N*-[4-(trifluoromethyl)benzyl]benzamide



C21-H19-F3-N2-O4-S; Mol wt: 452.45

ACTION – Hypoglycemic and hypolipidemic agent shown to decrease blood glucose levels by 43% in ob/ob mice at 10 mg/kg/day p.o. x 5 days. Another compound from this series of 2,4-dioxothiazolidine derivatives is:



265550: C22-H21-F3-N2-O4-S

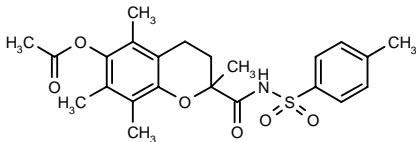
SOURCE – Kyorin.

REFERENCES

1. Nomura, M. et al. (Kyorin Pharm. Co., Ltd.) *N-Benzylidioxothiazolidylbenzamide derivs. and their preparation method*. JP 98087641.

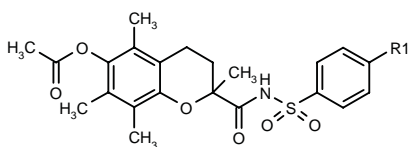
264677

6-Acetoxy-2,5,7,8-tetramethyl-*N*-(4-methylphenylsulfonyl)-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C23-H27-N-O6-S; Mol wt: 445.53

ACTION – Agent for the treatment of diabetes and diabetic complications with blood glucose-lowering activity, also reported to possess antioxidant properties and to have no toxicity. Other specifically claimed compounds from this series of benzopyran derivatives include the following:



Compound	R1	Formula
265211	Cl	C ₂₂ H ₂₄ ClNO ₆ S
265212	Br	C ₂₂ H ₂₄ BrNO ₆ S

SOURCE – ADIR.

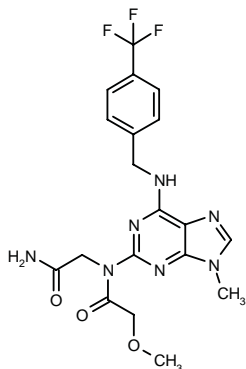
REFERENCES

1. Muller, T. et al. (ADIR et Cie.) *Benzopyran derivs., process for their preparation and pharmaceutical compsns. containing them*. EP 844245, JP 98158260.

CHIR-21208

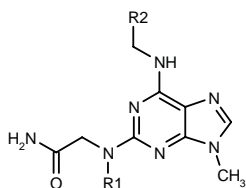
264847

N-(Carbamoylmethyl)-*N*-[9-methyl-*N*⁶-[4-(trifluoromethyl)benzyl]adenin-2-yl]-2-methoxyacetamide



C19-H20-F3-N7-O3; Mol wt: 451.41

ACTION – Glycogen synthase kinase 3 (GSK3) inhibitor (63% inhibition at 1 μM) with potential in the treatment of conditions mediated by GSK3 activity, particularly diabetes and Alzheimer's disease. A representative compound from a series of adenine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
CHIR-21172 [265691]	H	4-CF ₃ -Ph	C ₁₈ H ₁₆ F ₃ N ₇ O
CHIR-21232 [265692]	COCH ₂ NH ₂	4-CF ₃ -Ph	C ₁₈ H ₁₉ F ₃ N ₈ O ₂
CHIR-21220 [265693]	COEt	4-CF ₃ -Ph	C ₁₉ H ₂₀ F ₃ N ₇ O ₂
CHIR-20957 [265694]	H	2-Pyr	C ₁₄ H ₁₆ N ₈ O
CHIR-20981 [265695]	i-BuCO	2-Pyr	C ₁₉ H ₂₄ N ₈ O ₂
CHIR-21005 [265696]	COEt	2-Pyr	C ₁₇ H ₂₀ N ₈ O ₂
CHIR-21132 [265697]	COCH ₂ OMe	i-Bu	C ₁₈ H ₂₅ N ₇ O ₃

SOURCES – Univ. California, Oakland, CA (US); Chiron.

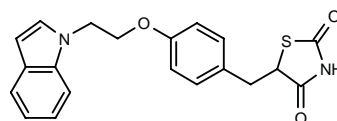
REFERENCES

1. Schultz, P. et al. (Chiron Corp.; Univ. California) *Purine inhibitors of glycogen synthase kinase 3 (GSK3)*. WO 9816528.

DRF-2189

264589

5-[4-[2-(1-Indolyl)ethoxy]benzyl]thiazoline-2,4-dione



C20-H18-N2-O3-S; Mol wt: 366.43

ACTION – Potent insulin sensitizer with euglycemic and hypolipidemic properties. DRF-2189 at doses of 10 and 100 mg/kg x 9 days administered via oral gavage decreased blood glucose (51-55 and 74%, respectively) and plasma triglyceride levels (77% at the dose of 100 mg/kg) in C57BL/KsJ-*db/db* mice. Similar results were obtained in C57BL/6J-*ob/ob* mice, where title compound (10 mg/kg x 14 days) also reduced both blood glucose and plasma triglyceride levels (51-59 and 53-55%, respectively). DRF-2189 showed good activity in an oral glucose tolerance test in both mouse strains. Pharmacokinetic studies after a single oral dose of 10 mg/kg in rats indicated that title compound was slowly absorbed and well distributed in various tissues (e.g., brown fat, skeletal muscle and heart), reaching high concentrations in target sites such as liver and subcutaneous fat.

SOURCE – Dr. Reddy's Res. Found., Hyderabad (IN).

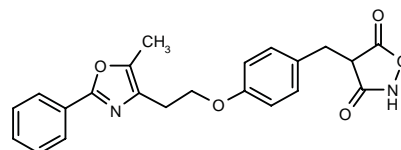
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- Fujita, T. et al. (Sankyo Co., Ltd.) *Hererocyclic cpds. having antidiabetic activity, their preparation and their use*. CA 2146701, EP 676398, JP 95330728, US 5624935.
- Jajoo, H.K. et al. *High-performance liquid chromatographic determination of the insulin sensitizing agent DRF-2189 in rat plasma*. J Chromatogr B 1998, 707(1-2): 241.
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- Lohray, B.B. et al. *Novel indole containing thiazolidinedione derivatives as potent euglycemic and hypolipidaemic agents*. Bioorg Med Chem Lett 1997, 7(7): 785.

JTT-501*

226594

4-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-isoxazolidine-3,5-dione



C22-H20-N2-O5; Mol wt: 392.41

ACTION – Orally active antidiabetic and hypolipidemic agent, an isoxazolidinedione that improves insulin resistance. In rats fed a high-fat diet, compound significantly improved insulin-induced GLUT4 translocation to the plasma membrane and insulin-induced glucose uptake. In Zucker fatty rats administered 100 mg/kg/day p.o. for 7 days, it potentiated insulin sensitivity; it also improved hypertriglyceridemia. Currently in clinical trials as a promising treatment for non-insulin-dependent diabetes mellitus.

SOURCES – Japan Tobacco; Pharmacia & Upjohn.

REFERENCES

- Shinkai, H. (Japan Tobacco, Inc.) *Isoxazolidinedione deriv. and use thereof*. EP 684242, JP 96517913, US 5728720, WO 9518125.
- Inoue, H. et al. *Influence of JTT-501, an insulin resistance improving agent, on glucose metabolism in rat liver*. J Jpn Diabetes Soc 1997, 40(Suppl. 1): Abst 3P 354.
- Komori, H. et al. *Improving effect of JTT-501, a new oral antidiabetic agent, on insulin resistance*. J Jpn Diabetes Soc 1997, 40(Suppl. 1): Abst 3V 06.
- Komori, T. et al. *Effect of JTT-501, a novel oral hypoglycemic agent, on insulin resistance. Studies in cultured human NIDDM skeletal muscle*. 34th Annu Meet Jpn Soc Clin Biochem Metab (April 18-19, Toyonaka) 1997, Abst 51.
- Komori, T. et al. *JTT-501 improves insulin resistance induced by glucosamine and TNF- α in cultured myotubes from human NIDDM skeletal muscle*. Diabetologia 1997, 40(Suppl. 1): Abst 1471.
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- JT announcing codevelopment agreement of new antidiabetic agents with a US venture business. Kagaku Kogyo Nippo 1996, September 24.
- Pharmacia & Upjohn licenses rights to novel JT diabetes drug. Prous Science Daily Essentials Juny 24, 1998.
- Japan Tobacco, Inc. Annual Report 1997.

*Identified compound **226594** Drug Data Rep 1996, 18(1): 60.

REPAGLINIDE⁺

Rec INN

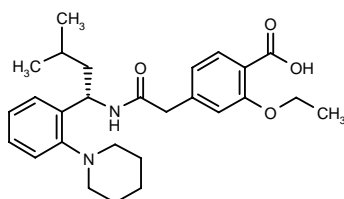
178930

(+)-2-Ethoxy-4-[N-[3-methyl-1(S)-[2-(1-piperidiny)]-phenyl]butyl]carbamoylmethyl]benzoic acid

AG-EE-388 (as racemic)

AG-EE-623 ZW

NN-623



C27-H36-N2-O4: Mol wt: 452.59

ACTION – Orally active, nonsulfonylurea antidiabetic agent of the meglitinide class that stimulates insulin secretion from pancreatic β -cells and shows a rapid onset and short duration of effect.

INDICATION – As an adjunct to diet and exercise to lower blood glucose in patients with non-insulin-dependent (type II) diabetes mellitus whose hyperglycemia can not be controlled satisfactorily with diet and exercise alone; for use in combination with metformin to lower blood glucose in patients whose hyperglycemia can not be controlled by exercise, diet and either repaglinide or metformin alone.

PRESENTATION – Tablets, 0.5, 1 and 2 mg.

PROPRIETARY NAME – Prandin (US).

SOURCES – Novo Nordisk; developed in collaboration with Boehringer Ingelheim and copromoted by Schering-Plough.

RECENT REFERENCES

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- Schwietert, R. et al. *No change in repaglinide pharmacokinetics with cimetidine coadministration*. Eur J Clin Pharmacol 1997, 52(Suppl.): Abst 431.
- Endocrinologic and Metabolic Drugs Advisory Committee meets in late November*. Prous Science Daily Essentials October 22, 1997.
- FDA advisory committee recommends approval for Prandin*. Prous Science Daily Essentials November 20, 1997.
- FDA approval obtained for Prandin*. Prous Science Daily Essentials December 29, 1997.
- Novo Nordisk and Schering-Plough announce copromotion agreement for PrandinTM and diabetes care products*. Novo Nordisk A/S/Schering-Plough Corp. 1998, January 28.
- Prandin introduced for treatment of type II diabetes in U.S.* Prous Science Daily Essentials June 3, 1998.
- PrandinTM, new oral treatment for type 2 diabetes, now available in the US*. Novo Nordisk Press Release 1998, June 8.

21. *Repaglinide gets expedited review status in U.S.* Prous Science Daily Essentials August 20, 1997.

22. *Repaglinide launch.* Novo Nordisk A/S Company Communication 1998, June 2.

23. *Schering-Plough to copromote Novo Nordisk's Prandin.* Prous Science Daily Essentials January 30, 1998.

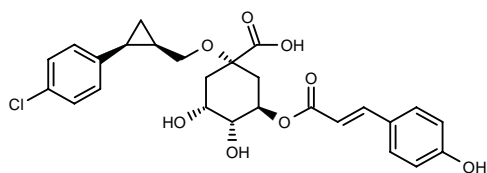
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MONOGRAPH – Graul, A. and Castañer, J. *Repaglinide*. Drugs Fut 1996, 21(7): 694.

S-3483

264724

(1*S*,3*R*,4*R*,5*R*)-1-[2(*S*)-(4-Chlorophenyl)-1(*R*)-cyclopropylmethoxy]-3,4-dihydroxy-5-[3-(4-hydroxyphenyl)-2(*E*)-propenyloxy]cyclohexane-1-carboxylic acid



C26-H27-Cl-O8; Mol wt: 502.95

ACTION – A potent, reversible and competitive inhibitor of the hepatic glucose-6-phosphatase system that specifically inhibits the T1 transporter protein, with no effect on the enzyme or pyrophosphatase activity. In primary rat hepatocyte cultures, S-3483 inhibited glucose production, and in isolated perfused rat liver, it inhibited both gluconeogenesis and glycogenolysis. In fed rats, an i.v. infusion of 50 mg/kg/h of S-3483 prevented the hyperglycemic peak induced by glucagon and subsequently lowered blood glucose levels. In fasted rats with normoglycemia maintained by gluconeogenesis, an i.v. infusion also produced a reduction in blood glucose levels. Potentially useful as a new approach to the treatment of non-insulin-dependent diabetes mellitus (NIDDM).

SOURCE – Hoechst Marion Roussel.

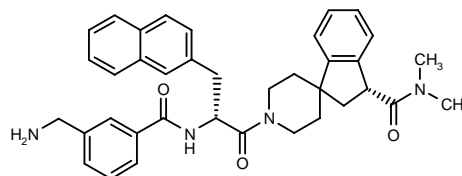
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

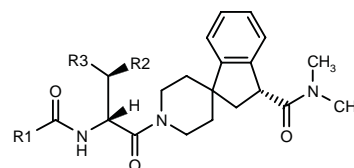
263822

1'-[2(*R*)-[3-(Aminomethyl)benzamido]-3-(2-naphthyl)-propionyl]-*N,N*-dimethylspiro[indane-1,4'-piperidine]-3(*R*)-carboxamide



C37-H40-N4-O3; Mol wt: 588.75

ACTION – Growth hormone secretagogue for the treatment of conditions characterized by a deficiency in growth hormone secretion such as short stature in children and osteoporosis, or for improving the repair of bone fracture. Within this series of piperidines, pyrrolidines and hexahydro-1*H*-azepines, the following are also included:



Compound	R1	R2	R3	Formula
264908	3-(NH ₂ CH ₂)-Ph	H	1-Naph	C ₃₇ H ₄₀ N ₄ O ₃
264909	(E)-CH=CHC(Me) ₂ NH ₂	Me	3-indolyl	C ₃₄ H ₄₃ N ₅ O ₃
264910	(E)-CH=CHC(Me) ₂ NH ₂	H	3-indolyl	C ₃₃ H ₄₁ N ₅ O ₃
264911	3-[NH ₂ C(Me) ₂]-Ph	Me	3-indolyl	C ₃₈ H ₄₆ N ₅ O ₃

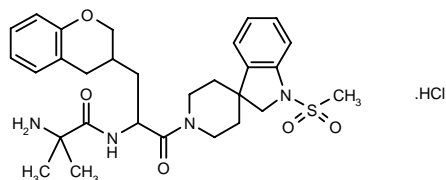
SOURCE – Merck & Co.

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264846

2-Amino-*N*-[2-(3,4-dihydro-2*H*-1-benzopyran-3-yl)-1-[1-(methanesulfonyl)spiro[indoline-3,4'-piperidin]-1'-ylcarbonyl]ethyl]-2-methylpropionamide hydrochloride



C29-H38-N4-O5-S.HCl; Mol wt: 591.16

ACTION – Potent promoter of the release of growth hormone (GH), as demonstrated in rats by a 2932% increase in GH release at 1 mg/kg i.v.

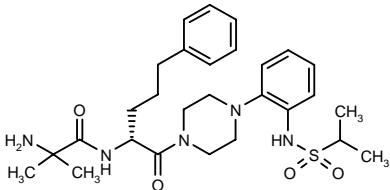
SOURCE – Fujisawa.

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264975

(*R*)-2-Amino-*N*-[2-[4-[2-(isopropylsulfonamido)phenyl]-piperazin-1-yl]-2-oxo-1-(3-phenylpropyl)ethyl]isobutyramide



C28-H41-N5-O4-S; Mol wt: 543.72

ACTION – Potent, orally active growth hormone (GH) secretagogue from a series of phenylpiperazines that displays an EC₅₀ of 2.8 nM in the rat pituitary cell assay.

SOURCE – Merck & Co.

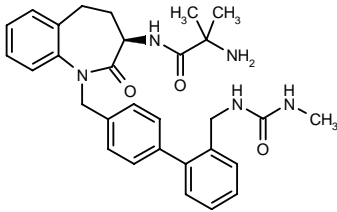
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L-739943

264592

2-Amino-2-methyl-*N*-[1-[2'-(3-methylureidomethyl)-biphenyl-4-ylmethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3(*R*)-yl]propionamide



C30-H35-N5-O3; Mol wt: 513.64

ACTION – Potent growth hormone (GH) secretagogue with an ED₅₀ of 1 nM in the *in vitro* rat pituitary cell assay. Oral efficacy was demonstrated in beagle dogs, with GH release at doses as low as 0.5 mg/kg p.o.; oral bioavailability in beagle dogs was estimated to be 23.8%.

SOURCE – Merck & Co.

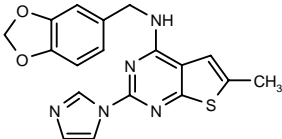
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TREATMENT OF MALE SEXUAL DYSFUNCTION

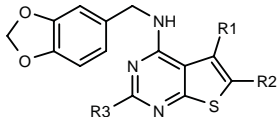
263262

4-(1,3-Benzodioxol-5-ylmethylamino)-2-(1-imidazolyl)-6-methylthieno[2,3-*d*]pyrimidine



C18-H15-N5-O2-S; Mol wt: 365.41

ACTION – Agent for the treatment of impotence and cardiovascular disorders, an inhibitor of phosphodiesterase type V (PDE V). Other specifically claimed thienopyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
263748	Me	Me	1-imidazolyl	C ₁₉ H ₁₇ N ₅ O ₂ S
263749	-(CH2)4-		1-imidazolyl	C ₂₁ H ₁₉ N ₅ O ₂ S
263750	Cl	H	1-imidazolyl	C ₁₇ H ₁₂ ClN ₅ O ₂ S
263751	H	Cl	1-imidazolyl	C ₁₇ H ₁₂ ClN ₅ O ₂ S
263752	-(CH2)4-		1,2,4-triazol-1-yl	C ₂₀ H ₁₈ N ₆ O ₂ S
263753	-(CH2)4-		1-pyrazolyl	C ₂₁ H ₁₉ N ₅ O ₂ S
263754	-(CH2)4-		3-Pyr	C ₂₃ H ₂₀ N ₄ O ₂ S

SOURCE – Merck KGaA.

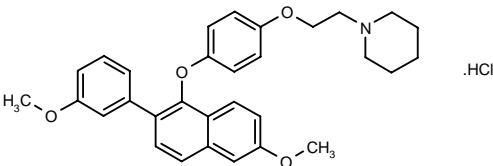
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TREATMENT OF GYNECOLOGICAL DISORDERS

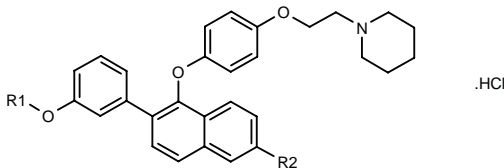
263335

1-[2-[4-[6-Methoxy-2-(3-methoxyphenyl)naphthalen-1-yloxy]phenoxy]ethyl]piperidine hydrochloride



C31-H33-N-O4.HCl; Mol wt: 520.07

ACTION – Agent for the treatment of postmenopausal syndrome and other estrogen-related pathological conditions including osteoporosis and hyperlipidemia. Efficacy was assessed in ovariectomized rats where the compound reduced serum cholesterol levels at doses of 0.01-1.0 mg/kg p.o., with a much lower effect on uterine weight than 17α-ethinylestradiol. Other specifically claimed naphthyl compounds include the following:



Compound	R1	R2	Formula
264137	Me	H	C ₃₀ H ₃₁ NO ₃ .HCl
264138	H	OH	C ₂₉ H ₂₉ NO ₄ .HCl
265391	H	H	C ₂₉ H ₂₉ NO ₃ .HCl
265392	H	OMe	C ₃₀ H ₃₁ NO ₄ .HCl
265393	Me	OH	C ₃₀ H ₃₁ NO ₄ .HCl

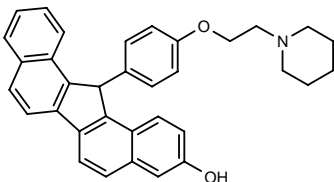
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly & Co.) *Naphthyl cpds., intermediates, compsns., and methods of use*. WO 9808797.

264658

13-[4-[2-(1-Piperidiny)ethoxy]phenyl]-13*H*-dibenzo[*a,l*]-fluoren-3-ol



C34-H31-N-O2; Mol wt: 485.62

ACTION – Agent for the treatment of postmenopausal syndrome including osteoporosis, cardiovascular disorders related to hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, it reduced serum cholesterol levels (46.9% at 0.1 mg/kg/day p.o.), with less stimulatory effect on the uterus compared to 17α-ethinylestradiol at the same dose.

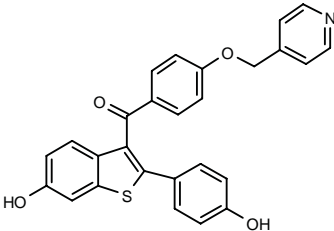
SOURCE – Lilly.

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1. Bryant, H.U. and Dodge, J.A. (Eli Lilly & Co.) *Naphthofluorene cpds., intermediates, compsns., and methods*. EP 832882, JP 98147559.

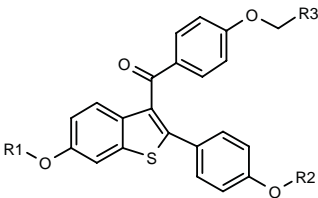
264662

1-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-1-[4-(4-pyridylmethoxy)phenyl]methanone



C27-H19-N-O4-S; Mol wt: 453.51

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disease related to hyperlipidemia and estrogen-dependent cancers, particularly breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, it significantly reduced serum cholesterol levels (48.3% at 0.1 mg/kg/day p.o.), with little stimulatory effect on the uterus compared to 17α-ethinylestradiol and no stimulatory effect on eosinophil infiltration into the uterus. Within this series of benzothiophene derivatives, the following are also included:



Compound	R1=R2	R3	Formula
265208	H	3-Pyr	C ₂₇ H ₁₉ NO ₄ S
265209	H	2-Pyr	C ₂₇ H ₁₉ NO ₄ S
265210	Me	3-thienyl	C ₂₈ H ₂₂ O ₄ S ₂

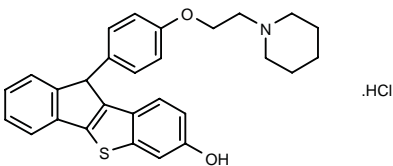
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly & Co.) *Benzothiophene cpds., compsns. and methods*. EP 832888.

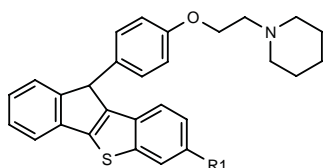
264663

10-[4-[2-(1-Piperidiny)ethoxy]phenyl]-10*H*-benz[*b*]indeno-[2,1-*d*]thiophen-7-ol hydrochloride



C28-H27-N-O2-S.HCl; Mol wt: 478.05

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders related to hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 1 and 10 mg/kg/day p.o., while increasing uterine weight to a lesser extent than 17 α -ethinylestradiol at 0.1 mg/kg/day; at these doses, compound was shown to produce much lower increases in uterus eosinophil infiltration than 17 α -ethinylestradiol. It was also shown to prevent bone loss in ovariectomized rats, and it inhibited the proliferation of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 10 nM. Within this series of benz[*b*]indeno[2,1-*d*]thiophene derivatives, the following are also included:



Compound	R1	Formula
265205	OMe	C ₂₉ H ₂₉ NO ₂ S
265206	H	C ₂₈ H ₂₇ NOS

SOURCE – Lilly.

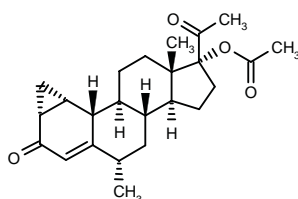
REFERENCES

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TX-525*

254232

17 α -Acetoxy-6 α -methyl-19-nor-1 β ,2 β -dihydrocyclopropa-[1,2]pregn-4-ene-3,20-dione



C24-H32-O4; Mol wt: 384.51

ACTION – Orally active synthetic progestin with high affinity and selectivity for the human progesterone receptor (K_d = 2.3 nM), devoid of estrogenic and androgenic potential. Compound displays some antiandrogenic activity and potent progestational, antiestrogenic and antiovarulatory effects in rats and rabbits. In female rats ovariectomized at midgestation, oral treatment with TX-525 on days 10-19 was able to maintain pregnancy with an ED₅₀ of about 0.1 mg/day. In normally cycling female rats, orally administered compound inhibited ovulation, and in ovariectomized rats, it inhibited estradiol-induced vaginal cornification; in male rats it exhibited some antiandrogenic activity.

SOURCE – Theramex.

REFERENCES

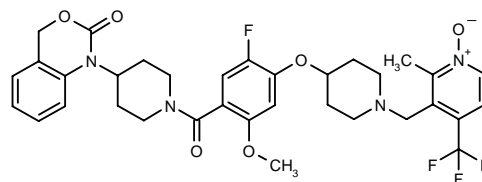
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2. Delansorne, R. et al. *In vivo reproductive endocrinological profile of TX 525, a new orally active synthetic progestin*. 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, Abst 108.
3. Delansorne, R. et al. *Steroid receptor profile of TX 525, a new synthetic progestin*. 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, Abst 107.

*Identified compound **254232** Drug Data Rep 1997, 19(10): 916.

UTERINE STIMULANTS AND TOCOLYTICS

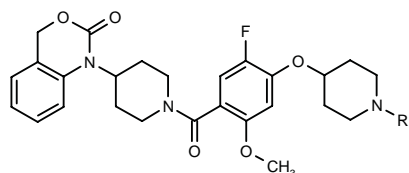
264044

1-[1-[5-Fluoro-2-methoxy-4-[1-[2-methyl-1-oxido-4-(tri-fluoromethyl)pyridin-3-ylmethyl]piperidin-4-yloxy]-benzoyl]piperidin-4-yl]-2,4-dihydro-1*H*-3,1-benzoxazin-2-one



C34-H36-F4-N4-O6; Mol wt: 672.68

ACTION – Agent for the treatment of preterm labor, dysmenorrhea and for stopping labor prior to cesarean delivery, an oxytocin receptor antagonist. Other specifically claimed benzoxazine compounds include the following:



Compound	R1	Formula
264598	4-CF3-1-oxido-3-Pyr	C ₃₃ H ₃₄ F ₄ N ₄ O ₆
264599	1-oxido-5,6,7,8-tetrahydro-5-quinolyl	C ₃₅ H ₃₉ FN ₄ O ₆

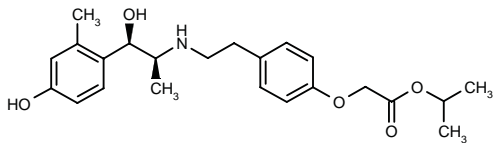
SOURCE – Merck & Co.

REFERENCES

1. Bell, I.M. et al. (Merck & Co., Inc.) *Tocolytic oxytocin receptor antagonists*. US 5756497.

264379

(1*S*,2*R*)-2-[4-[2-[2-Hydroxy-2-(4-hydroxy-2-methylphenyl)-1-methylethylamino]ethyl]phenoxy]acetic acid isopropyl ester



C23-H31-N-O5; Mol wt: 401.50

ACTION – Selective β_2 -adrenoceptor agonist (EC_{50} = 30 nM in pregnant rat uterus) with reduced effects on the heart. No mortality was observed following a single administration of 50 mg/kg i.v. to mice. Potentially useful for preventing preterm labor and threatened abortion, and as a bronchodilator.

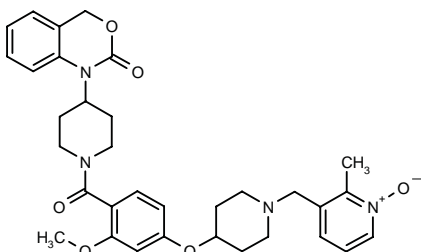
SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharm. Co., Ltd.) 2-Amino-1-(4-hydroxy-2-methylphenyl)propanol derivs. WO 9813333.

L-372662***221893**

1-[1-[2-Methoxy-4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]benzoyl]piperidin-4-yl]-2,4-dihydro-1*H*-3,1-benzoxazin-2-one



C33-H38-N4-O6; Mol wt: 586.69

ACTION – Oxytocin (OT) antagonist with good water solubility for the treatment of preterm labor either by the i.v. or oral route. Compound displays high affinity for the OT receptor, with a K_i of 4.1 nM for the cloned human OT receptor and a K_i of 15 nM for the rat receptor, and selectivity relative to human arginine vasopressin receptors (K_i = 2500 and 28,000 nM for V_{1a} and V_2 receptors, respectively). *In vivo*, it demonstrated good potency against OT-stimulated rat uterus contractions following both i.v. and i.d. administration (AD_{50} = 0.71 and 5.2 mg/kg, respectively), and excellent oral bioavailability in rats (90%) and dogs (96%).

SOURCE – Merck & Co.

REFERENCES

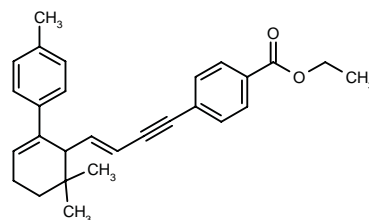
1. Bock, M.G. et al. (Merck & Co., Inc.) Benzoxazinone and benzopyrimidinone piperidinyl tocolytic oxytocin receptor antagonists. EP 714299, JP 97500134, US 5665719, WO 9502405.

2. Bell, I.M. et al. Development of orally active oxytocin antagonists: Studies on 1-(1-[4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl]piperidin-4-yl)-1,4-dihydrobenz[d][1,3]oxazin-2-one (L-372,662) and related pyridines. J Med Chem 1998, 41(12): 2146.

*Identified compound **221893** (see **219408**) Drug Data Rep 1995, 17(6): 548.

DERMATOLOGIC DRUGS**ANTIPSORIATICS****264481**

4-[4-(3,3,4'-Trimethyl-2,3,4,5-tetrahydrobiphenyl-2-yl)but-3(*E*)-en-1-ynyl]benzoic acid ethyl ester



C28-H30-O2; Mol wt: 398.54

ACTION – Agent for the treatment of psoriasis, acne or as an antidote to retinoid or vitamin A overdose or poisoning. Compound displays retinoid-inverse agonist activity, as demonstrated in a holoreceptor transactivation assay in CV1 cells (IC_{50} = 1.0 nM). A representative compound within a series of aryl- and heteroarylcyclohexenyl substituted alkenes.

Certain compounds within the scope of the invention exhibit retinoid-like or retinoid-antagonist activity.

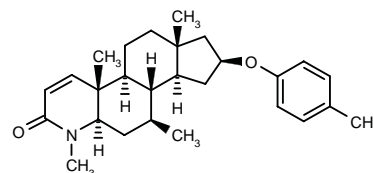
SOURCE – Allergan.

REFERENCES

1. Beard, R.L. et al. (Allergan) Aryl- and heteroarylcyclohexenyl subst. alkenes having retinoid agonist, antagonist or inverse agonist type biological activity. US 5760276.

ACNE THERAPY**L-762943****265238**

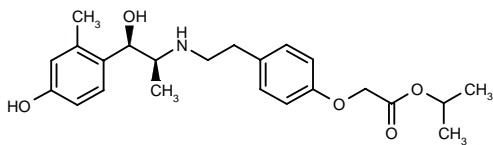
16 β -(4-Methylphenoxy)-4,7 β -dimethyl-4-aza-5 α -androst-1-en-3-one



C27-H37-N-O2; Mol wt: 407.59

264379

(1*S*,2*R*)-2-[4-[2-[2-Hydroxy-2-(4-hydroxy-2-methylphenyl)-1-methylethylamino]ethyl]phenoxy]acetic acid isopropyl ester



C23-H31-N-O5; Mol wt: 401.50

ACTION – Selective β_2 -adrenoceptor agonist (EC_{50} = 30 nM in pregnant rat uterus) with reduced effects on the heart. No mortality was observed following a single administration of 50 mg/kg i.v. to mice. Potentially useful for preventing preterm labor and threatened abortion, and as a bronchodilator.

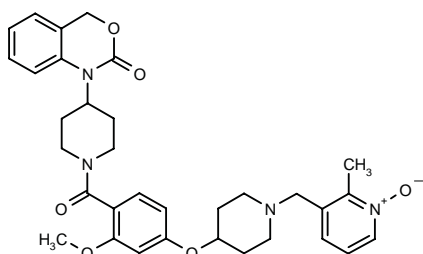
SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharm. Co., Ltd.) 2-Amino-1-(4-hydroxy-2-methylphenyl)propanol derivs. WO 9813333.

L-372662***221893**

1-[1-[2-Methoxy-4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]benzoyl]piperidin-4-yl]-2,4-dihydro-1*H*-3,1-benzoxazin-2-one



C33-H38-N4-O6; Mol wt: 586.69

ACTION – Oxytocin (OT) antagonist with good water solubility for the treatment of preterm labor either by the i.v. or oral route. Compound displays high affinity for the OT receptor, with a K_i of 4.1 nM for the cloned human OT receptor and a K_i of 15 nM for the rat receptor, and selectivity relative to human arginine vasopressin receptors (K_i = 2500 and 28,000 nM for V_{1a} and V_2 receptors, respectively). *In vivo*, it demonstrated good potency against OT-stimulated rat uterus contractions following both i.v. and i.d. administration (AD_{50} = 0.71 and 5.2 mg/kg, respectively), and excellent oral bioavailability in rats (90%) and dogs (96%).

SOURCE – Merck & Co.

REFERENCES

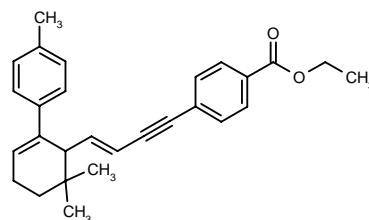
1. Bock, M.G. et al. (Merck & Co., Inc.) Benzoxazinone and benzopyrimidinone piperidinyl tocolytic oxytocin receptor antagonists. EP 714299, JP 97500134, US 5665719, WO 9502405.

2. Bell, I.M. et al. Development of orally active oxytocin antagonists: Studies on 1-(1-[4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl]piperidin-4-yl)-1,4-dihydrobenz[d][1,3]oxazin-2-one (L-372,662) and related pyridines. J Med Chem 1998, 41(12): 2146.

*Identified compound **221893** (see **219408**) Drug Data Rep 1995, 17(6): 548.

DERMATOLOGIC DRUGS**ANTIPSORIATICS****264481**

4-[4-(3,3,4'-Trimethyl-2,3,4,5-tetrahydrobiphenyl-2-yl)but-3(*E*)-en-1-ynyl]benzoic acid ethyl ester



C28-H30-O2; Mol wt: 398.54

ACTION – Agent for the treatment of psoriasis, acne or as an antidote to retinoid or vitamin A overdose or poisoning. Compound displays retinoid-inverse agonist activity, as demonstrated in a holoreceptor transactivation assay in CV1 cells (IC_{50} = 1.0 nM). A representative compound within a series of aryl- and heteroarylcyclohexenyl substituted alkenes.

Certain compounds within the scope of the invention exhibit retinoid-like or retinoid-antagonist activity.

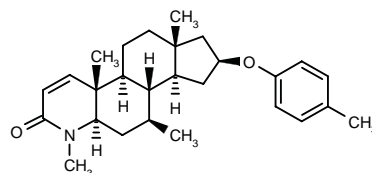
SOURCE – Allergan.

REFERENCES

1. Beard, R.L. et al. (Allergan) Aryl- and heteroarylcyclohexenyl substd. alkenes having retinoid agonist, antagonist or inverse agonist type biological activity. US 5760276.

ACNE THERAPY**L-762943****265238**

16 β -(4-Methylphenoxy)-4,7 β -dimethyl-4-aza-5 α -androst-1-en-3-one



C27-H37-N-O2; Mol wt: 407.59

ACTION – Antiacne agent that potently inhibits the type 1 isozyme of human 5 α -reductase with selectivity over other steroid-binding enzymes and receptors including type 2 5 α -reductase.

SOURCE – Merck & Co.

REFERENCES

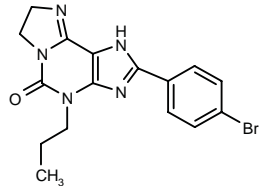
1. Durette, P.L. et al. (Merck & Co., Inc.) *16-Substd.-4-aza-androstane 5- α -reductase isozyme 1 inhibitors*. EP 724592, JP 97511213, WO 9511254.

2. Sahoo, S. et al. *16 β -(4-Tolyloxy)-4,7 β -dimethyl-4-aza-5 α -androstan-1-ene-3-one (L-762,943): A new type 1 selective 5 α -reductase inhibitor*. 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, Abst 37.

MISCELLANEOUS
DERMATOLOGIC DRUGS

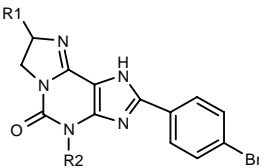
264440

2-(4-Bromophenyl)-4-propyl-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*f*]purin-5-one

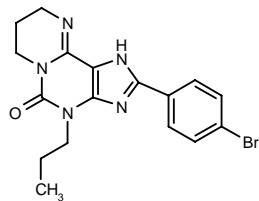


C16-H16-Br-N5-O; Mol wt: 374.24

ACTION – Antipruritic, antiasthmatic and bronchodilating agent, an adenosine A₃ receptor antagonist shown to inhibit compound 48/80-induced pruritus in mice with an ED₅₀ value of 96.5 mg/kg p.o. No deaths were observed following oral administration of 1000 mg/kg to mice. Other compounds from this series of fused purine derivatives include the following:



Compound	R1	R2	Formula
265397	Et	Pr	C ₁₈ H ₂₀ BrN ₅ O
265398	H	Bu	C ₁₇ H ₁₈ BrN ₅ O
265399	(R)-i-Pr	Pr	C ₁₉ H ₂₂ BrN ₅ O



265396: C17-H18-Br-N5-O

SOURCE – Kyowa Hakko.

REFERENCES

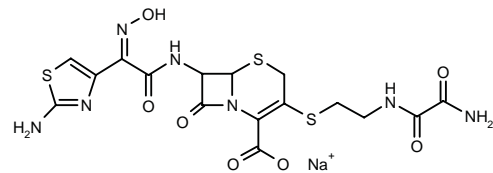
1. Tsumuki, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Fused purine derivs*. WO 9815555.

ANTIINFECTIVE THERAPY

β -LACTAM ANTIBIOTICS

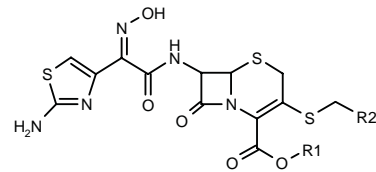
264359

7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-(2-oxamidoethylsulfanyl)-3-cephem-4-carboxylic acid sodium salt



C16-H16-N7-Na-O7-S3; Mol wt: 537.51

ACTION – Cephalosporin antibacterial agent active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P (MIC = 0.39 μ g/ml) and *Escherichia coli* NIHJ (MIC = 0.2 μ g/ml). It displayed good urinary recovery in mice after oral administration (65% recovery after 20 mg/kg p.o.). Other related compounds include the following:



Compound	R1	R2	Formula
265568	Na ⁺	CH2NH ₂ SO2NH2	C ₁₄ H ₁₆ N ₇ NaO ₇ S ₄
265569	Na ⁺	CH2NH ₂ SO2CH2Cl	C ₁₅ H ₁₆ ClN ₈ NaO ₇ S ₄
265570	H	C(=NH)NH2	C ₁₄ H ₁₅ N ₇ O ₅ S ₃
265571	Na ⁺	CH=CHCH=NOH	C ₁₆ H ₁₅ N ₆ NaO ₆ S ₃

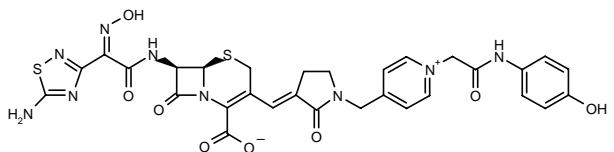
SOURCE – Toyama.

REFERENCES

1. Takagi, H. et al. (Toyama Chem. Co., Ltd.) *Novel cephalosporin derivs. or their salts and medicines containing them*. JP 98101680.

265147

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[(*E*)-1-[1-[*N*-(4-hydroxyphenyl)carbamoylmethyl]pyridinium-4-ylmethyl]-2-oxopyrrolidin-3-ylidenemethyl]-3-cephem-4-carboxylate



C30-H27-N9-O8-S2; Mol wt: 705.72

ACTION – Antiacne agent that potently inhibits the type 1 isozyme of human 5α-reductase with selectivity over other steroid-binding enzymes and receptors including type 2 5α-reductase.

SOURCE – Merck & Co.

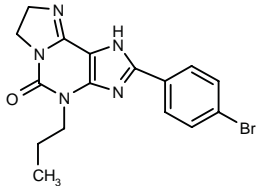
REFERENCES

1. Durette, P.L. et al. (Merck & Co., Inc.) 16-Substd.-4-aza-androstane 5-α-reductase isozyme 1 inhibitors. EP 724592, JP 97511213, WO 9511254.
2. Sahoo, S. et al. 16β-(4-Tolyloxy)-4,7β-dimethyl-4-aza-5α-androstan-1-ene-3-one (L-762,943): A new type 1 selective 5α-reductase inhibitor. 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, Abst 37.

MISCELLANEOUS
DERMATOLOGIC DRUGS

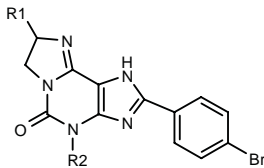
264440

2-(4-Bromophenyl)-4-propyl-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*f*]purin-5-one

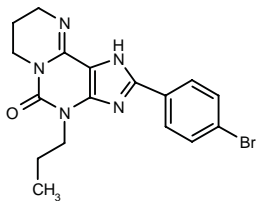


C16-H16-Br-N5-O; Mol wt: 374.24

ACTION – Antipruritic, antiasthmatic and bronchodilating agent, an adenosine A₃ receptor antagonist shown to inhibit compound 48/80-induced pruritus in mice with an ED₅₀ value of 96.5 mg/kg p.o. No deaths were observed following oral administration of 1000 mg/kg to mice. Other compounds from this series of fused purine derivatives include the following:



Compound	R1	R2	Formula
265397	Et	Pr	C ₁₈ H ₂₀ BrN ₅ O
265398	H	Bu	C ₁₇ H ₁₈ BrN ₅ O
265399	(R)-i-Pr	Pr	C ₁₉ H ₂₂ BrN ₅ O



265396: C17-H18-Br-N5-O

SOURCE – Kyowa Hakko.

REFERENCES

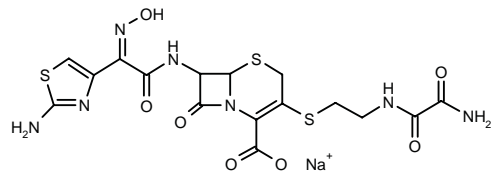
1. Tsumuki, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) Fused purine derivs. WO 9815555.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

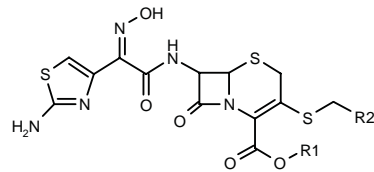
264359

7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-(2-oxamidoethylsulfanyl)-3-cephem-4-carboxylic acid sodium salt



C16-H16-N7-Na-O7-S3; Mol wt: 537.51

ACTION – Cephalosporin antibacterial agent active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P (MIC = 0.39 μg/ml) and *Escherichia coli* NIHJ (MIC = 0.2 μg/ml). It displayed good urinary recovery in mice after oral administration (65% recovery after 20 mg/kg p.o.). Other related compounds include the following:



Compound	R1	R2	Formula
265568	Na ⁺	CH2NH ₂ SO2NH2	C ₁₄ H ₁₆ N ₇ NaO ₇ S ₄
265569	Na ⁺	CH2NH ₂ SO2CH2Cl	C ₁₅ H ₁₆ ClN ₈ NaO ₇ S ₄
265570	H	C(=NH)NH2	C ₁₄ H ₁₅ N ₇ O ₅ S ₃
265571	Na ⁺	CH=CHCH=NOH	C ₁₆ H ₁₅ N ₆ NaO ₆ S ₃

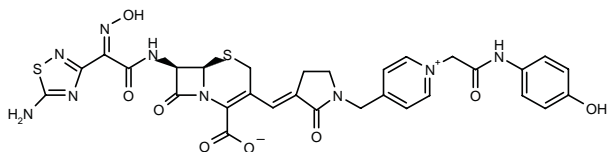
SOURCE – Toyama.

REFERENCES

1. Takagi, H. et al. (Toyama Chem. Co., Ltd.) Novel cephalosporin derivs. or their salts and medicines containing them. JP 98101680.

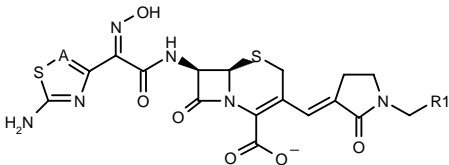
265147

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[(*E*)-1-[1-[*N*-(4-hydroxyphenyl)carbamoylmethyl]pyridinium-4-ylmethyl]-2-oxopyrrolidin-3-ylidenemethyl]-3-cephem-4-carboxylate



C30-H27-N9-O8-S2; Mol wt: 705.72

ACTION – Cephalosporin antibacterial agent with potent and broad-spectrum activity, particularly against methicillin-resistant staphylococci (MRSA), enterococci and pneumococci. MIC values against methicillin-sensitive *Staphylococcus aureus* 6538 and methicillin-resistant *S. aureus* 42080 were 0.5 and 4 µg/ml, respectively. Within this series of cephalosporin pyridinium derivatives, the following are also included:



Compound	R1	A	Formula
265839	1-(4-OH-PhNHCOCH2)-4-Pyr	CH	C ₃₁ H ₂₈ N ₈ O ₈ S ₂
265840	1-(3-F-4-OH-PhNHCOCH2)-4-Pyr	CH	C ₃₁ H ₂₇ FN ₈ O ₈ S ₂
265841	1-(3-F-4-OH-PhNHCOCH2)-4-Pyr	N	C ₃₀ H ₂₆ FN ₈ O ₈ S ₂
265842	1-(3-Cl-4-OH-PhNHCOCH2)-4-Pyr	CH	C ₃₁ H ₂₇ ClN ₈ O ₈ S ₂
265843	1-(3-MeO-4-OH-PhNHCOCH2)-4-Pyr	CH	C ₃₂ H ₃₀ N ₈ O ₉ S ₂
265844	1-(3-F-4-OH-PhNHCOCH2)-3-Pyr	CH	C ₃₁ H ₂₇ FN ₈ O ₈ S ₂

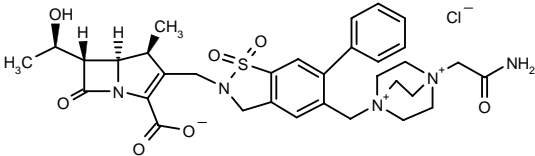
SOURCE – Roche.

REFERENCES

1. Angehrn, P. et al. (F. Hoffmann-La Roche AG) *Pyridinium-substd. (lactamylvinyl)-cephalosporin derivs., their preparation and their use as antibiotics*. EP 838465, JP 98120687.

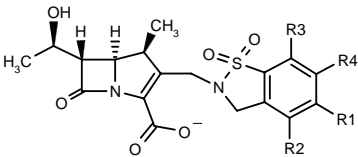
263827

(1*S*,5*R*,6*S*)-2-[5-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]oct-1-ylmethyl]-6-phenyl-2,3-dihydro-1,2-benzisothiazol-2-ylmethyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate chloride *S,S*-dioxide

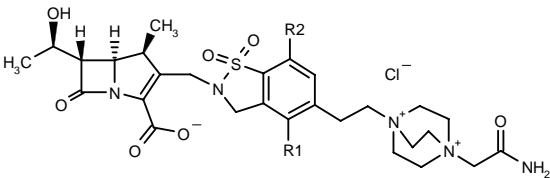


C33-H40-Cl-N5-O7-S; Mol wt: 686.22

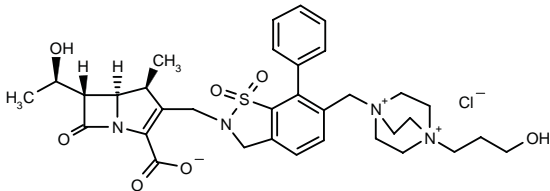
ACTION – Carbapenem antibiotic active against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS). Within this series of specifically claimed carbapenems, the following are also included:



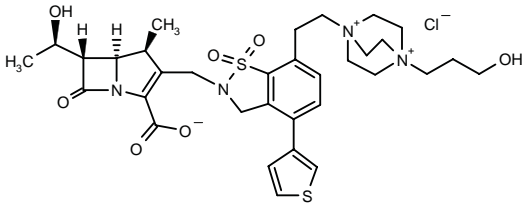
Compound	R1	R2	R3	R4	Formula
264900	3-Me-1-imidazolyl-CH2	Ph	H	H	C ₂₉ H ₃₀ N ₄ O ₆ S
264901	3-Me-1-imidazolyl-CH2CH2	H	2-thienyl	H	C ₂₈ H ₃₀ N ₄ O ₆ S ₂
264905	3-Me-1-imidazolyl-CH2CH2	H	Ph	H	C ₃₀ H ₃₂ N ₄ O ₆ S
264906	3-Me-1-imidazolyl	H	H	Ph	C ₂₉ H ₃₀ N ₄ O ₆ S
264907	3-Me-1-imidazolyl	Ph	H	H	C ₂₈ H ₂₈ N ₄ O ₆ S



Compound	R1	R2	Formula
264902	H	3-furyl	C ₃₁ H ₃₈ ClN ₅ O ₈ S
264904	Ph	H	C ₃₄ H ₄₂ ClN ₅ O ₇ S



264899: C34-H43-Cl-N4-O7-S



264903: C33-H43-Cl-N4-O7-S2

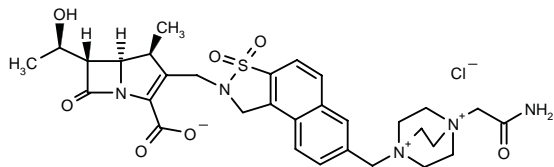
SOURCE – Merck & Co.

REFERENCES

1. Cama, L.D. et al. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment*. WO 9810761.

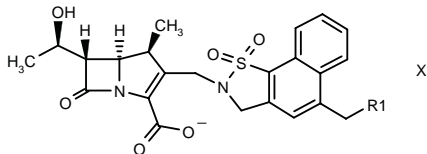
263860

(1*S*,5*R*,6*S*)-2-[7-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]octan-1-ylmethyl]-1,2-dihydronaphth-[1,2-*d*]isothiazol-2-ylmethyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate chloride *S,S*-dioxide

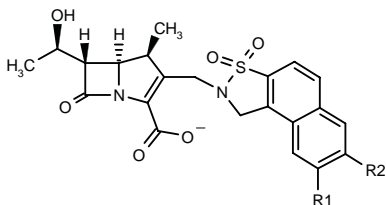


C31-H38-Cl-N5-O7-S; Mol wt: 660.18

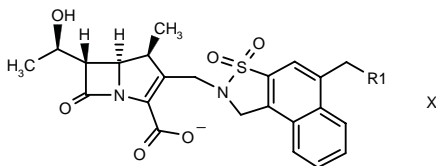
ACTION – Carbapenem antibiotic active against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant coagulase-negative staphylococci (MRCNS), and to a lesser extent against Gram-negative bacteria. Compound is reported to be more stable against dehydropeptidases than other related compounds. Other specifically claimed compounds from this series of carbapenems include the following:



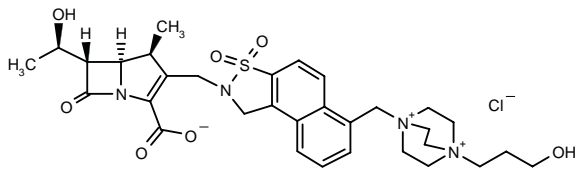
Compound	R1	X	Formula
265182	4-[OH(CH2)3]-1,4-diazoniabicyclo[2.2.2]oct-1-yl	Cl ⁻	C ₃₂ H ₄₁ ClN ₄ O ₇ S
265184	3-Me-1-imidazolyl-CH2		C ₂₈ H ₃₀ N ₄ O ₆ S



Compound	R1	R2	Formula
265183	3-Me-1-imidazolyl-CH2CH2	H	C ₂₈ H ₃₀ N ₄ O ₆ S
265189	1,3-(Me)2-2-imidazolyl	H	C ₂₈ H ₃₀ N ₄ O ₆ S
265190	H	3-Me-1-imidazolyl-CH2	C ₂₇ H ₂₈ N ₄ O ₆ S



Compound	R1	R2	Formula
265185	4-(CH2CONH2)-1,4-diazoniabicyclo[2.2.2]oct-1-yl-CH2	Cl ⁻	C ₃₂ H ₄₀ ClN ₅ O ₇ S
265187	4-(NH2COCH2)-1,4-diazoniabicyclo[2.2.2]oct-1-yl	Cl ⁻	C ₃₁ H ₃₈ ClN ₅ O ₇ S
265188	3-Me-1-imidazolyl		C ₂₇ H ₂₈ N ₄ O ₆ S



265186: C32-H41-Cl-N4-O7-S

SOURCE – Merck & Co.

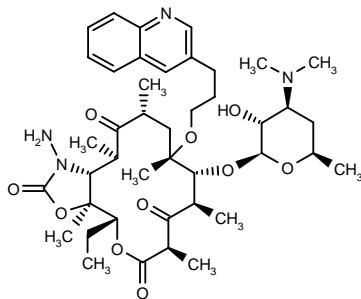
REFERENCES

1. Cama, L.D. et al. (Merck & Co., Inc.) *Carbapenem antibacterial cpds., compsns. containing such cpds. and methods of treatment.* WO 9811108.

MISCELLANEOUS ANTIBIOTICS

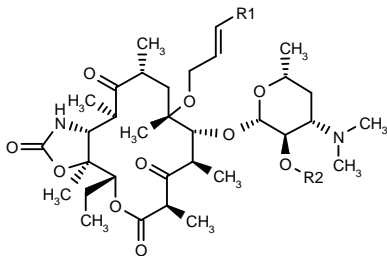
263812

(1*S*,2*R*,5*R*,7*R*,8*R*,9*R*,11*R*,13*R*,14*R*)-15-Amino-2-ethyl-1,5,7,9,11,13-hexamethyl-9-[3-(3-quinolyl)propoxy]-8-[3,4,6-trideoxy-3-(dimethylamino)-β-D-glucopyranosyloxy]-3,17-dioxa-15-azabicyclo[12.3.0]heptadecane-4,12,16-trione



C42-H62-N4-O10; Mol wt: 782.97

ACTION – Semisynthetic macrolide (ketolide) anti-bacterial agent reported to possess improved acid stability relative to erythromycin A, active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* ATCC 6538P (MIC = 0.01 µg/ml vs. 0.2 µg/ml for erythromycin A) and *Escherichia coli* SS (MIC = 0.1 µg/ml vs. 0.78 µg/ml for erythromycin A). Other compounds from this series of 6-*O*-substituted ketolides include the following:



Compound	R1	R2	Formula
265173	3-quinolinyl	H	C ₄₂ H ₅₉ N ₃ O ₁₀
265174	5-indolyl	H	C ₄₁ H ₅₉ N ₃ O ₁₀
265175	3-NO ₂ -Ph	H	C ₃₉ H ₅₇ N ₃ O ₁₂
265176	6-quinolyl	H	C ₄₂ H ₅₉ N ₃ O ₁₀
265177	6-NO ₂ -3-quinolyl	H	C ₄₂ H ₅₈ N ₄ O ₁₂
265178	5-quinolyl	H	C ₄₂ H ₅₉ N ₃ O ₁₀
265179	2-Me-6-quinolyl	H	C ₄₃ H ₆₁ N ₃ O ₁₀
265180	3-quinolinyl	Ac	C ₄₄ H ₆₁ N ₃ O ₁₁
265181	5-isoquinolyl	H	C ₄₂ H ₅₉ N ₃ O ₁₀

SOURCE – Abbott.

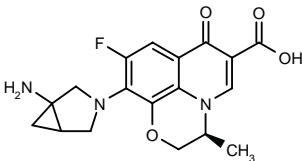
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MISCELLANEOUS
ANTIBACTERIAL DRUGS

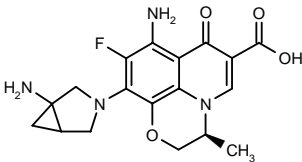
264391

10-(1-Amino-3-azabicyclo[3.1.0]hexan-3-yl)-9-fluoro-3(S)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid



C18-H18-F-N3-O4; Mol wt: 359.36

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria and reported to exhibit a favorable profile *in vivo* and high safety. *In vitro* it was highly active against *Escherichia coli* NIHJ and *Proteus vulgaris* 08601 (MIC = 0.003 µg/ml or less), *Pseudomonas aeruginosa* 32121 (MIC = 0.05 µg/ml), *Staphylococcus aureus* 209P (MIC = 0.006 µg/ml) and *Streptococcus pyogenes* G-36 (MIC = 0.05 µg/ml). Another compound from this series of pyridobenzoxazine derivatives is:



265440: C18-H19-F-N4-O4

SOURCE – Daiichi Pharm.

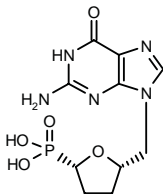
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1. Takemura, M. et al. (Daiichi Pharm. Co., Ltd.) Pyridobenzoxazine derivs. WO 9813370.

ANTIVIRAL DRUGS

262309

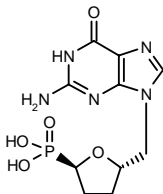
(S,S)-9-(5-Phosphonetetrahydrofuran-2-ylmethyl)guanine



C10-H14-N5-O5-P; Mol wt: 315.22

[α]_D +52 ° (c 0.10, H2O).

ACTION – Agent with good potency and selectivity against human cytomegalovirus (HCMV), a nucleotide phosphonate analog proven effective *in vitro* in two infected human cell lines (IC₅₀ = 0.5-1 µg/ml and CC₅₀ = 10-50 µg/ml in Wi38 cells; IC₅₀ = 0.58 µg/ml and CC₅₀ = 55 µg/ml in Hs38 cells); it was equipotent to ganciclovir. Title compound was also effective *in vivo* in protecting MCMV-infected mice from death (complete protection following 2.5-20 mg/kg i.p. t.i.d. for 4 days), although it was toxic at the dose of 40 mg/kg on this schedule. The *trans*-isomer displays a similar *in vitro* profile:



262310: C10-H14-N5-O5-P

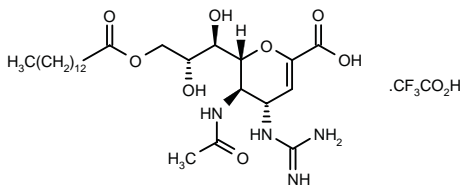
SOURCES – BioChem Therapeutic; Glaxo Wellcome.

REFERENCES

- 1. Nguyen-Ba, N. et al. *Anti-viral cpds.* US 5789394.
- 2. Chan, L. et al. *Identification of novel nucleotide phosphonate analogs with potent anti-HCMV activity.* 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 034.
- 3. Nguyen-Ba, N. et al. *Identification of novel nucleotide tetrahydrofuranyl phosphonate analogues with potent anti-HCMV activity.* Antivir Res 1998, 37(3): Abst 153.

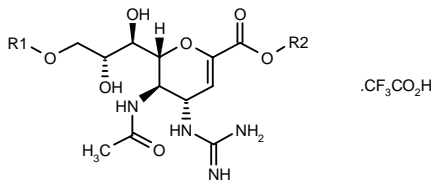
263257

(4*S*,5*R*,6*R*)-5-Acetamido-6-[3-tetradecanoyloxy-1(*R*),2(*R*)-dihydroxypropyl]-4-ureido-5,6-dihydro-4*H*-pyran-2-carboxylic acid trifluoroacetate



C26-H46-N4-O8.C2-H-F3-O2; Mol wt: 656.70

ACTION – Antiviral agent for the treatment and prevention of influenza virus infections with excellent sialidase (neuraminidase)-inhibitory activity. It completely protected mice infected with influenza virus from death at 6 and 8 days after infection when given at a dose of 0.3 μmol/kg intranasally. Within this series of neuraminic acid derivatives, the following are also included:



Compound	R1	R2	Formula
263759	COC5H11	H	C ₁₈ H ₃₀ N ₄ O ₈ .C ₂ HF ₃ O ₂
263760	COC7H15	H	C ₂₀ H ₃₄ N ₄ O ₈ .C ₂ HF ₃ O ₂
263761	COC9H19	H	C ₂₂ H ₃₈ N ₄ O ₈ .C ₂ HF ₃ O ₂
263762	H	C18H37	C ₃₀ H ₅₆ N ₄ O ₇ .C ₂ HF ₃ O ₂

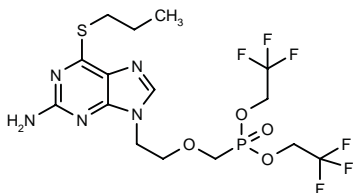
SOURCE – Sankyo.

REFERENCES

1. Honda, T. et al. (Sankyo Co., Ltd.) *Neuraminic acid cpds.* JP 98109981, WO 9806712.

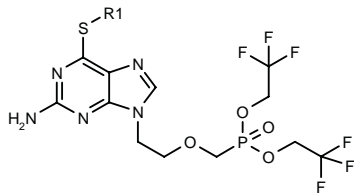
263263

2-[2-Amino-6-(propylsulfanyl)purin-9-yl]ethoxymethyl]-phosphonic acid bis(2,2,2-trifluoroethyl) ester



C15-H20-F6-N5-O4-P-S; Mol wt: 511.38

ACTION – Antiviral agent with potent *in vitro* activity against hepatitis B virus, as determined by the ability to inhibit HBV DNA synthesis (IC₅₀ = 0.02 μM), and low cytotoxic potential (CC₅₀ > 1000 μM). Compound was also active *in vivo*, producing 49% inhibition of HBV DNA synthesis when given to infected mice at a dose of 0.2 g/kg p.o. Within this series of phosphonate nucleotide compounds, the following are also included:



Compound	R1	Formula
263704	Et	C ₁₄ H ₁₈ F ₆ N ₅ O ₄ PS
263705	i-Pr	C ₁₅ H ₂₀ F ₆ N ₅ O ₄ PS

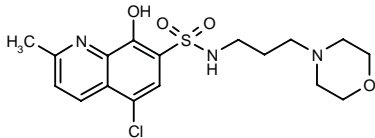
SOURCE – Mitsubishi Chem.

REFERENCES

1. Ubasawa, M. et al. (Mitsubishi Chem. Corp.) *Phosphonate nucleotide cpds.* WO 9806726.

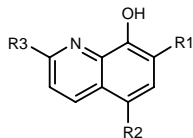
263841

5-Chloro-8-hydroxy-2-methyl-*N*-[3-(4-morpholinyl)-propyl]quinoline-7-sulfonamide



C17-H22-Cl-N3-O4-S; Mol wt: 399.89

ACTION – Antiviral agent found to be particularly active against herpesviruses and cytomegalovirus (CMV), with an IC₅₀ against human CMV ranging from 2.5 to 3.6 μM. Within this series of specifically claimed 2-hydroxy-7-substituted quinoline derivatives, the following are also included:



Compound	R1	R2	R3	Formula
264806	6-Cl-2-benzo-thiazolyl-NHCO	H	H	C ₁₇ H ₁₀ ClN ₃ O ₂ S
264807	2-Pyr-CH2NHSO2	Cl	Me	C ₁₆ H ₁₄ ClN ₃ O ₃ S
264808	SO2NH(CH2)4Ph	Cl	Me	C ₂₀ H ₂₁ ClN ₃ O ₃ S
264809	2-Pyr-CH2CH2NHSO2	Cl	Me	C ₁₇ H ₁₆ ClN ₃ O ₃ S

Some compounds within the scope of the invention act by virtue of their CMV polymerase-inhibitory activity.

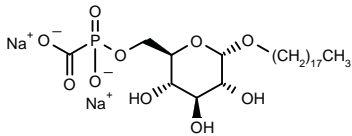
SOURCE – Pharmacia & Upjohn.

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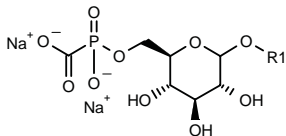
264851

Hydroxy(1-*O*-octadecyl- α -D-glucopyranos-6-*O*-yl)-phosphorylformic acid disodium salt

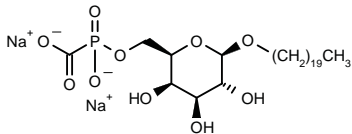


C25-H47-Na2-O10-P; Mol wt: 584.59

ACTION – Antiviral agent for the treatment or prevention of infections caused by herpesviruses and retroviruses such as herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and HIV-1 and HIV-2. Within this series of phosphonoformic acid derivatives, the following are also included:



Compound	R1	Isomer	Formula
265698	(Z)-(CH2)8CH=CHC8H17	α	C ₂₅ H ₄₈ Na ₂ O ₁₀ P
265699	(E)-(CH2)8CH=CHC8H17	α	C ₂₅ H ₄₈ Na ₂ O ₁₀ P
265700	C14H29	α	C ₂₁ H ₃₉ Na ₂ O ₁₀ P
265701	C14H29	β	C ₂₁ H ₃₉ Na ₂ O ₁₀ P
265702	C12H25	α	C ₁₉ H ₃₅ Na ₂ O ₁₀ P



265703: C27-H51-Na2-O10-P

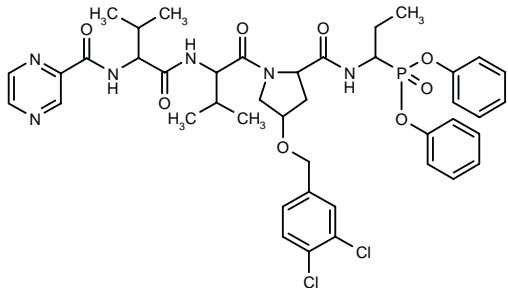
SOURCE – Astra.

REFERENCES

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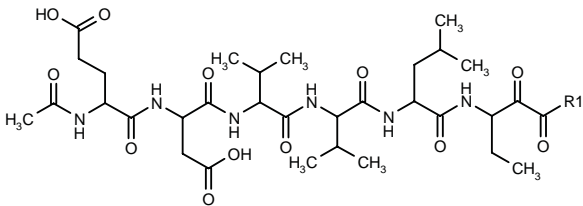
264892

1-[Pyrazin-2-ylcarbonyl-DL-valyl-DL-valyl-DL-[4-(3,4-dichlorobenzyloxy)prolylamino]propylphosphonic acid diphenyl ester

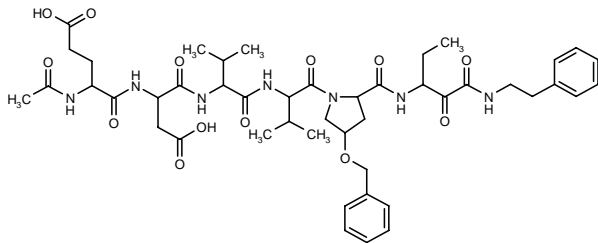


C42-H49-Cl2-N6-O8-P; Mol wt: 867.76

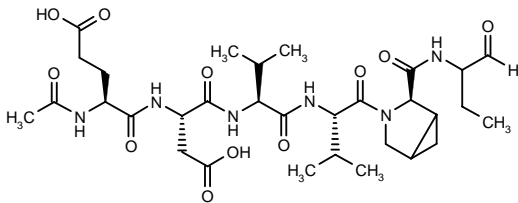
ACTION – Agent for the treatment of hepatitis C that acts by inhibiting hepatitis C virus NS3 protease ($K_i < 1 \mu\text{M}$). Other representative compounds include the following:



Compound	R1	Formula
265830	OH	C ₃₂ H ₅₂ N ₆ O ₁₃
265831	NHCH2Ph	C ₃₉ H ₅₉ N ₇ O ₁₂
265832	2-MeO-PhCH2NH	C ₄₀ H ₆₁ N ₇ O ₁₃
265833	NHCH2CH2Ph	C ₄₀ H ₆₁ N ₇ O ₁₂
265834	NHP _r	C ₃₅ H ₅₉ N ₇ O ₁₂
265835	NHCH(Me)CH2OMe	C ₃₆ H ₆₁ N ₇ O ₁₃
265836	4-Pyr-CH2NH	C ₃₈ H ₅₈ N ₆ O ₁₂
265837	2-THF-CH2NH	C ₃₇ H ₆₁ N ₇ O ₁₃



265829: C46-H63-N7-O13



265838: C31-H48-N6-O11

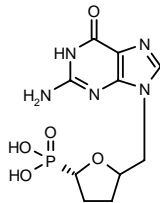
SOURCE – Vertex.

REFERENCES

1. Tung, R.D. et al. (Vertex Pharm., Inc.) *Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease.* WO 9817679.

265422

(-)-5-(Guanin-9-ylmethyl)tetrahydrofuran-2(S)-phosphonic acid



C10-H14-N5-O5-P; Mol wt: 315.22

ACTION – Antiviral agent, a guanine phosphonate analog active against human cytomegalovirus (HCMV; IC_{50} = 0.08-0.09 μ g/ml); clinical isolates of HCMV resistant to ganciclovir remained sensitive to compound. In mice with experimentally induced CMV infection, it prevented or prolonged mean time to death at doses of 1.0-10.0 mg/kg/day; compound demonstrated comparable or superior activity to HPMPG, as well as decreased nephrotoxicity.

SOURCE – BioChem Therapeutic.

REFERENCES

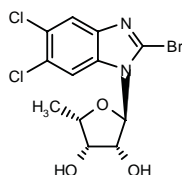
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1. Bedard, J. et al. *Anticytomegaloviral activity and toxicity studies of (-)-2(S)-dihydroxyphosphinoyl-5-(guanin-9'-yl)methyltetrahydrofuran, a novel guanine phosphonate analogue.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 60291.

1325

263126

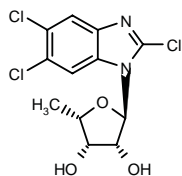
2-Bromo-5,6-dichloro-1*H*-benzimidazol-1-yl 5-deoxy- α -L-lyxofuranoside



C12-H11-Br-Cl2-N2-O3; Mol wt: 382.04

Solid, m.p. 125-7 °C.

ACTION – Antiviral agent that acts by inhibiting viral DNA synthesis. Compound was active against human cytomegalovirus, giving an IC_{50} value of 0.4 μ M in the plaque assay and an IC_{90} value of 2.0 μ M in the yield reduction assay, but it was inactive against herpes simplex virus type 1 (HSV-1; IC_{50} > 100 μ M). It also displayed low cytotoxicity in stationary HFF cells and growing KB cells, with IC_{50} values of 32 and 60 μ M, respectively. Another furanosylbenzimidazole is:



1311 [263137]: C12-H11-Cl3-N2-O3

SOURCE – Glaxo Wellcome.

REFERENCES

1. Chamberlain, S.D. et al. (Glaxo Group, Ltd.) *Therapeutic cpds.* WO 9725337.

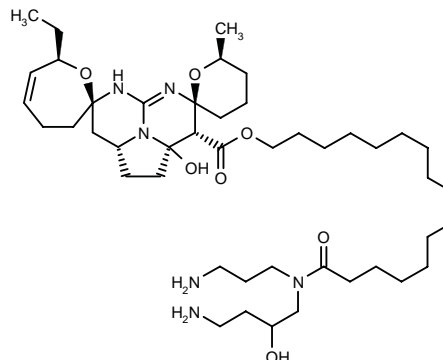
2. Drach, J.C. et al. *Benzimidazole L-sugar nucleosides: Large biological changes from small structural modifications.* *Antivir Res* 1998, 37(3): Abst 105.

3. Migawa, M. *Design, synthesis, and antiviral activity of α -nucleosides: D- And L-isomers of lyxofuranosyl- and (5-deoxylyxofuranosyl) benzimidazoles.* *J Med Chem* 1998, 41(8): 1242.

CAMBRESCIDIN 816

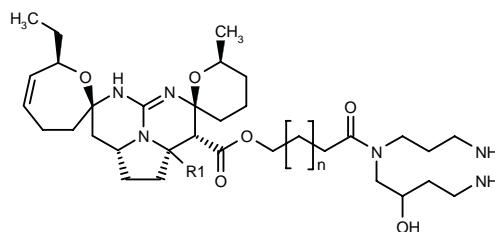
264057

(2*R*,2'*a*,2''*S*,6''*S*,7*R*,8'*S*,8'*a**R*)-7-Ethyl-8'*a*-hydroxy-6''-methyl-2,2',2'*a*,3,3',4,4',5',7,7',8',8'*a*-dodecahydro-1'*H*,2''*H*-dispiro[oxepin-2,4',5',6',8b'-triazacenaphthylene-7',2''-pyran]-8'-carboxylic acid 15-[*N*-(4-amino-2-hydroxybutyl)-*N*-(3-aminopropyl)carbamoyl]pentadecyl ester



C45-H80-N6-O7; Mol wt: 817.16

ACTION – Antiviral and antineoplastic agent isolated from the sponge *Crambe crambe*, reported to completely inhibit herpes simplex virus type 1 (HSV-1) *in vitro* at a concentration of 1.25 μ g/well and to inhibit by 98% the growth of murine leukemia L1210 cells at 0.1 μ g/ml. Other compounds isolated from the same source include the following:



Compound	R1	n	Formula
Cambrescidin 830 [264120]	OH	14	C ₄₆ H ₈₂ N ₆ O ₇
Cambrescidin 844 [264121]	OH	15	C ₄₇ H ₈₄ N ₆ O ₇
Cambrescidin 800 [264122]	H	13	C ₄₅ H ₈₀ N ₆ O ₆

SOURCE – PharmaMar.

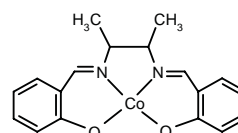
REFERENCES

1. Rinehart, K.L. and Jares-Erijman, E.A. (PharmaMar, SA) *Crambescidins: New antiviral and cytotoxic cpds. from the sponge Crambe crambe.* US 5756734.

RD3-0174

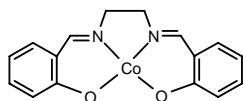
263618

[(*E*,*E*)-2,2'-(3,4-Dimethyl-2,5-diazahepta-1,5-dien-1,6-diyl- κ N², κ N⁵)bis(phenolato- κ O)(2-)]cobalt

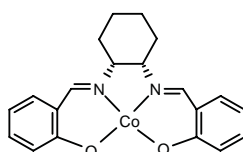


C18-H18-Co-N2-O2; Mol wt: 353.29

ACTION – Antiviral agent, a potent and selective human cytomegalovirus (HCMV) protease inhibitor (IC_{50} = 1.66 μ M). Effects on the replication of HCMV were demonstrated in the virus-induced plaque formation assay in MRC-5 cells, giving an EC_{50} of 2.65 μ M against laboratory strain AD169 and of 2.44-3.48 μ M against clinical isolates, and it showed low cytotoxic activity (CC_{50} = 40.5 μ M). Other related compounds include the following:



RD3-0171 [265537]: C16-H14-Co-N2-O2



RD3-0178 [263619]: C20-H20-Co-N2-O2

SOURCE – Rational Drug Design Lab., Fukushima (JP).

REFERENCES

1. Watanabe, S. et al. *Inhibition of human cytomegalovirus proteinase by salcomine derivatives*. Antivir Res 1998, 37(3): Abst 155.
2. Watanabe, S. et al. *Inhibition of human cytomegalovirus proteinase by salcomine derivatives*. Antivir Chem Chemother 1998, 9(3): 269.

REBETRON™

266041

Combination of interferon alfa-2b and ribavirin

ACTION – A combination of recombinant interferon alfa-2b for injection (*Intron® A*) and oral ribavirin (*Rebetol™*).

INDICATION – Treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following interferon alfa therapy.

PRESENTATION – Combination packages containing *Rebetol™* 200-mg capsules and *Intron® A* as follows: vials (0.5 ml) containing 3 million IU of interferon alfa-2b, recombinant; multidose vials (3.8 ml) containing a total of 22.8 million IU of interferon alfa-2b, recombinant (3 million IU/0.5 ml), providing delivery of 6 0.5-ml doses containing 3 million IU of *Intron® A* (for a label strength of 18 million IU); and multidose pen (1.5 ml) containing a total of 22.5 million IU of interferon alfa-2b, recombinant (3 million IU/0.2 ml), providing delivery of 6 0.2-ml doses containing 3 million IU of *Intron® A* (for a label strength of 18 million IU).

PROPRIETARY NAME – *Rebetron* (US).

SOURCE – Schering-Plough (oral ribavirin is exclusively licensed from ICN for the treatment of hepatitis C).

RECENT REFERENCES

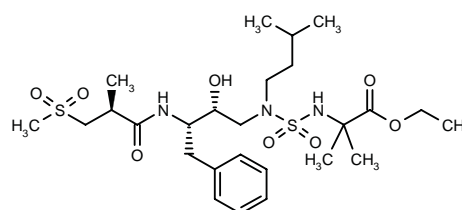
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2. *FDA approves new combination therapy product for HCV*. Prous Science Daily Essentials June 4, 1998.

3. *FDA clears new hepatitis C treatment for marketing*. FDA Press Release 1998, June 3.
4. *Rebetron launch*. Schering-Plough Corp. Company Communication 1998, June 5.
5. *Rebetron now available in the U.S*. Prous Science Daily Essentials June 9, 1998.
6. *Schering-Plough submits NDA for intron A + ribavirin*. Prous Science Daily Essentials December 10, 1997.

AIDS MEDICINES

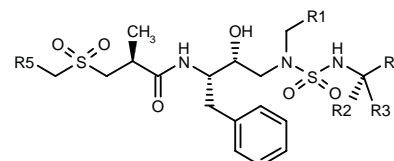
264045

N-[*N*-[2(*R*)-Hydroxy-3(*S*)-[2(*S*)-methyl-3-(methylsulfonyl)propionamido]-4-phenylbutyl]-*N*-(3-methylbutyl)-sulfamoyl]-2-methylalanine ethyl ester



C26-H45-N3-O8-S2; Mol wt: 591.78

ACTION – Antiviral agent for AIDS, an inhibitor of retroviral proteases, particularly HIV protease. Other specifically claimed sulfonylalkanoylamino hydroxyethylamino sulfonylurea derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
264600	i-Bu	Me	H	CO2H	H	C ₂₃ H ₃₉ N ₃ O ₈ S ₂
264601	4-Pyr	Me	Me	CO2H	H	C ₂₅ H ₃₆ N ₄ O ₈ S ₂
264602	i-Bu	Me	Me	CO2H	H	C ₂₄ H ₄₁ N ₃ O ₈ S ₂
264603	i-Bu	-(CH2)4-		CO2H	H	C ₂₆ H ₄₃ N ₃ O ₈ S ₂
264604	i-Bu	Me	Me	CO2Me	H	C ₂₅ H ₄₃ N ₃ O ₈ S ₂
264605	i-Bu	CH2CO2H	Me	Me	H	C ₂₅ H ₄₃ N ₃ O ₈ S ₂
264606	i-Pr	Me	Me	CO2H	CH2Ph	C ₃₀ H ₄₅ N ₃ O ₈ S ₂
264607	i-Pr	CH(Me)-CO2H	H	H	H	C ₂₃ H ₃₉ N ₃ O ₈ S ₂
264608	4-F-Ph	-CH2CH2-		CO2H	H	C ₂₆ H ₃₄ FN ₃ O ₈ S ₂
264609	i-Pr	Me	Me	CH2OH	H	C ₂₃ H ₄₁ N ₃ O ₇ S ₂

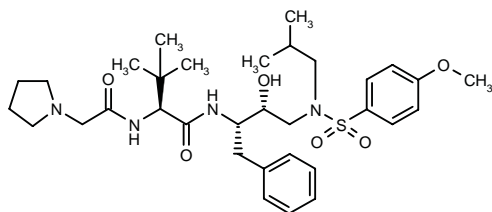
SOURCE – Searle.

REFERENCES

1. Vazquez, M.L. et al. (G.D. Searle & Co.) *Sulfonylalkanoylamino hydroxyethylamino sulfonyl urea derivs. useful as retroviral protease inhibitors*. US 5756498.

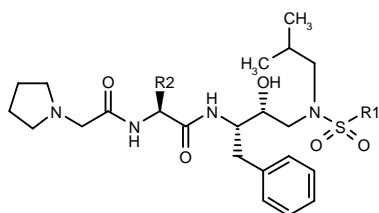
264053

N-[1(*S*)-Benzyl-2(*R*)-hydroxy-3-[*N*-isobutyl-*N*-(4-methoxyphenylsulfonyl)amino]propyl]-3,3-dimethyl-2(*S*)-[2-(1-pyrrolidinyl)acetamido]butyramide



C33-H50-N4-O6-S; Mol wt: 630.84

ACTION – Antiviral agent for AIDS, an inhibitor of HIV protease ($IC_{50} = 3$ nM) with potent anti-HIV activity in infected CEM cells ($EC_{50} = 5$ nM). A representative compound from a series of amino acid hydroxyethyl-aminosulfonamide derivatives, wherein the following are also included:



Compound	R1	R2	Formula
264638	1,3-benzodioxol-5-yl	i-Pr	C ₃₂ H ₄₆ N ₄ O ₇ S
264639	2-(NHCO2Me)-5-benzimidazolyl	t-Bu	C ₃₅ H ₅₁ N ₇ O ₇ S
264640	6-benzothiazolyl	t-Bu	C ₃₃ H ₄₇ N ₅ O ₅ S ₂
264641	4-MeO-Ph	(<i>S</i>)-CH(Me)Et	C ₃₃ H ₅₀ N ₄ O ₆ S
264642	1,3-benzodioxol-5-yl	C(Me)2SO2Me	C ₃₃ H ₄₈ N ₄ O ₉ S ₂
264643	2,3-dihydro-5-benzofuranyl	t-Bu	C ₃₄ H ₅₀ N ₄ O ₆ S
264644	1,3-benzodioxol-5-yl	ethynyl-CH2	C ₃₂ H ₄₂ N ₄ O ₇ S
264645	4-MeO-Ph	i-Pr	C ₃₂ H ₄₈ N ₄ O ₆ S
265630	1,3-benzodioxol-5-yl	t-Bu	C ₃₃ H ₄₈ N ₄ O ₇ S
265631	1,3-benzodioxol-5-yl	(<i>S</i>)-CH(Me)Et	C ₃₃ H ₄₈ N ₄ O ₇ S
265632	1,3-benzodioxol-5-yl	CH2SO2Me	C ₃₁ H ₄₄ N ₄ O ₉ S ₂
265633	Ph	t-Bu	C ₃₂ H ₄₈ N ₄ O ₅ S

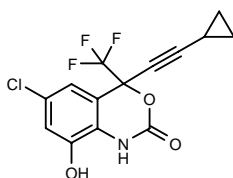
SOURCE – Searle.

REFERENCES

1. Getman, D.P. et al. (G.D. Searle & Co.) *Amino acid hydroxyethylamino sulfonamide retroviral protease inhibitors*. US 5756533.

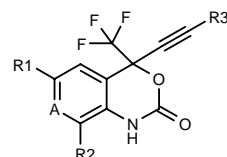
264409

(±)-6-Chloro-4-(cyclopropylethynyl)-8-hydroxy-4-(trifluoromethyl)-2,4-dihydro-1*H*-3,1-benzoxazin-2-one



C14-H9-Cl-F3-N-O3; Mol wt: 331.68

ACTION – Antiviral agent for AIDS, an inhibitor of HIV reverse transcriptase. A representative compound from a series of benzoxazinones, wherein the following are also specifically claimed:



Compound	R1	R2	R3	A	Isomer	Formula
265809	Cl	OH	cyclopropyl	CH	(-)	C ₁₄ H ₉ ClF ₃ NO ₃
265810	Ac	H	cyclopropyl	CH	racemic	C ₁₆ H ₁₂ F ₃ NO ₃
265811	Cl	H	cyclopropyl	N	racemic	C ₁₃ H ₈ ClF ₃ N ₂ O ₂
265812	Cl	H	2-furyl	CH	racemic	C ₁₅ H ₇ ClF ₃ NO ₃
265813	OMe	H	Et	CH	racemic	C ₁₄ H ₁₂ F ₃ NO ₃
265814	Cl	H	1-D-cyclopropyl	N	racemic	C ₁₃ H ₇ ClF ₃ N ₂ O ₂

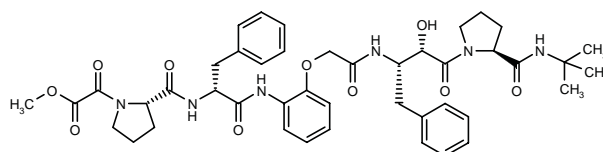
SOURCE – DuPont Merck (now DuPont Pharm.).

REFERENCES

1. Christ, D.D. et al. (The Du Pont Merck Pharm. Co.) *4,4-Disubst.-1,4-dihydro-2H-3,1-benzoxazin-2-ones useful as HIV reverse transcriptase inhibitors and intermediates and processes for making the same*. WO 9814436.

264584

1-[2(*S*)-Hydroxy-3(*S*)-[2-[2-[1-(methoxalyl)-L-prolyl-D-phenylalaninamido]phenoxy]acetamido]-4-phenylbutyryl]-L-proline *tert*-butylamide



C44-H54-N6-O10; Mol wt: 826.94

White powder, m.p. 105-7 °C; $[\alpha]_D^{28} -41.3^\circ$ (c 0.6, CHCl₃).

ACTION – Antiviral agent for AIDS, a dipeptide-type HIV protease inhibitor derived from KNI-102 ($IC_{50} = 0.90$ µg/ml) with a binding site for gp120.

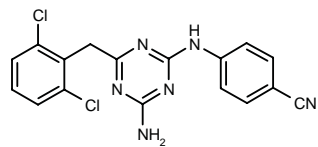
SOURCE – Univ. Shizuoka, Shizuoka (JP).

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1. Asagarsu, A. et al. *Synthesis of dipeptide-type human immunodeficiency virus (HIV) protease inhibitors with a binding unit to GP120*. Chem Pharm Bull 1998, 46(5): 867.
2. Asagarsu, A. et al. *Synthesis of dipeptide-type HIV protease inhibitor having a binding site to gp120*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst 1-P-07.

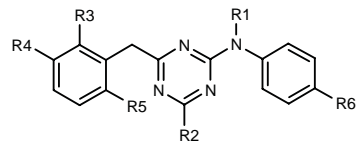
264667

4-[4-Amino-6-(2,6-dichlorobenzyl)-1,3,5-triazin-2-yl-amino]benzonitrile



C17-H12-Cl2-N6; Mol wt: 371.23

ACTION – Antiviral agent for AIDS with potent anti-HIV-1 activity in infected MT-4 cells ($IC_{50} = 0.002 \mu M$), but very low cytotoxicity in uninfected cells ($CC_{50} > 100 \mu M$; selectivity index $> 42,553$). Compound is reported to be active against HIV-1 strains that have become resistant to known non-nucleoside reverse transcriptase inhibitors. It is also reported to have little or no binding affinity for human α_1 -acid glycoprotein. Within this series of substituted diamino-1,3,5-triazines, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
265214	H	NHMe	Cl	H	Cl	CN	C ₁₈ H ₁₄ Cl ₂ N ₆
265215	H	NHC(=NH)Me	Cl	H	Cl	CN	C ₁₉ H ₁₆ Cl ₂ N ₇
265216	Ac	NHAc	Cl	H	Cl	CN	C ₂₁ H ₁₆ Cl ₂ N ₆ O ₂
265217	H	NH2	Cl	Cl	Cl	CN	C ₁₇ H ₁₁ Cl ₃ N ₆
265218	H	NH2	H	Me	Me	CN	C ₁₉ H ₁₈ N ₆
265219	H	N=CHN(Me)2	Cl	H	Cl	H	C ₁₉ H ₁₈ Cl ₂ N ₆

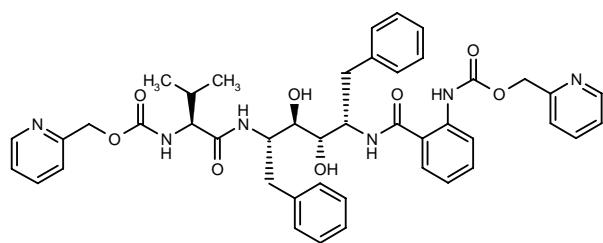
SOURCE – Janssen.

REFERENCES

1. Kukla, M.J. et al. (Janssen Pharm. NV) *Substd. diamino-1,3,5-triazine derivs.* EP 834507, JP 98114759.

265000

N-[2-[N-[1(S)-Benzyl-2(S),3(R)-dihydroxy-5-phenyl-4(S)-(2-pyridylmethoxycarbonyl-L-valylamino)pentyl]-carbamoyl]phenyl]carbamic acid 2-pyridylmethyl ester



C44-H48-N6-O8; Mol wt: 788.90

ACTION – Antiviral agent for AIDS, an inhibitor of HIV-1 protease ($K_i = 3 \text{ pM}$) with potent anti-HIV activity in infected CEM cells ($EC_{50} = 6 \text{ nM}$) and low cytotoxicity in uninfected CEM cells ($IC_{50} > 100 \mu M$), being similar or superior in potency to currently available compounds such as indinavir ($K_i = 4 \text{ pM}$, $EC_{50} = 50 \text{ nM}$), ritonavir ($K_i = 9.3 \text{ pM}$, $EC_{50} = 36 \text{ nM}$) and saquinavir ($K_i = 7 \text{ pM}$, $EC_{50} = 10 \text{ nM}$).

SOURCE – Dept. Health Human Services (US).

REFERENCES

1. Randad, R.S. et al. (Dept. Health Human Services [USA]) *Retroviral agents containing anthranilamide, substd. benzamide and other subunits, and methods of using same.* US 5763464.

TREATMENT OF PROTOZOAL DISEASES

NYVAC-Pf7

264761

Vaccine consisting of 7 Plasmodium falciparum full-length or nearly full-length genes inserted into the NYVAC vector; the malaria genes are: the sporozoite-stage antigens CS and sporozoite surface protein 2 (SSP2); the liver-stage antigen LSA1; the asexual blood-stage proteins MSP1, AMA1 and SERA; and the sexual-stage antigen Pfs25

vP1209

ACTION – Multistage, multiantigen malaria vaccine consisting of an attenuated vaccinia virus (NYVAC) with 7 *Plasmodium falciparum* genes inserted into the genome, encoding proteins from all stages of the parasite's life cycle. In a phase I/IIa trial in human volunteers, antibody responses were poor, but cellular immune responses were detected in $> 90\%$ of the volunteers. Of 35 volunteers bitten by *P. falciparum*-infected mosquitoes, 1 was completely protected and there was a significant delay in time to parasite patency in the other volunteers compared to controls.

SOURCES – Pasteur Merieux Connaught; Virogenetics; Walter Red Army Inst. Res., Washington, DC (US).

REFERENCES

1. Paoletti, E. et al. (Virogenetics Corp.) *Malaria recombinant poxvirus vaccine.* WO 9428930.

2. Ockenhouse, C.F. et al. *Phase I/IIa safety, immunogenicity, and efficacy trial of NYVAC-Pf7, a pox-vectored, multiantigen, multistage vaccine candidate for Plasmodium falciparum malaria.* J Infect Dis 1998, 177(6): 1664.

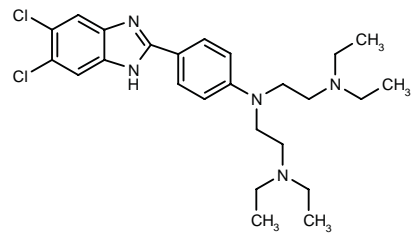
3. Tine, J.A. et al. *NYVAC-Pf7: A poxvirus-vectored, multiantigen, multistage vaccine candidate for Plasmodium falciparum malaria.* Infect Immun 1996, 64(9): 3822.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

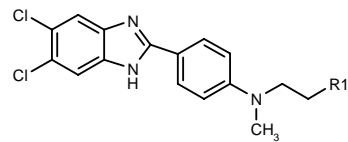
263252

N-[4-(5,6-Dichlorobenzimidazol-2-yl)phenyl]-N,N-bis[2-(diethylamino)ethyl]amine



C25-H35-Cl2-N5; Mol wt: 476.49

ACTION – Agent for the treatment of inflammation, atherosclerosis, restenosis and immune disorders such as arthritis and transplant rejection, a monocyte chemoattractant protein-1 (MCP-1) antagonist that inhibits the binding of MCP-1 to its receptor, as demonstrated in a binding assay by an IC₅₀ value of 11.1 μM for inhibition of the binding of [¹²⁵I]-MCP-1 in human monocytic THP-1 cell membranes. At 10 μM, compound produced 62-142% inhibition of MCP-1-induced chemotaxis of human T-lymphocyte blast cells. In addition, it was found to be active in a glucan-induced pulmonary granulomatous vasculitis model in rats following oral administration and was shown to potently inhibit the recruitment of T-cells in a cutaneous delayed hypersensitivity model in rats at 30 mg/kg p.o. Within this series of 2-phenylbenzimidazole derivatives, the following are also included:



Compound	R1	Formula
263766	1-Pip	C ₂₁ H ₂₄ Cl ₂ N ₄
263767	N(Et)2	C ₂₀ H ₂₄ Cl ₂ N ₄

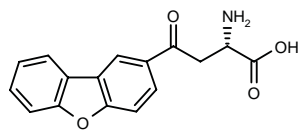
SOURCE – Warner-Lambert.

REFERENCES

1. Connor, D.T. et al. (Warner-Lambert Co.) 2-Phenyl benzimidazole derivs. as MCP-1 antagonists. WO 9806703.

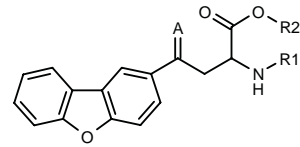
263256

2(S)-Amino-4-(dibenzofuran-2-yl)-4-oxobutyric acid

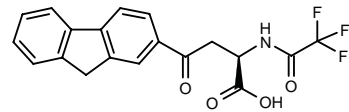


C16-H13-N-O4; Mol wt: 283.28

ACTION – Agent for the treatment of arthritis and osteoporosis that acts by inhibiting matrix metalloproteinases such as gelatinase (IC₅₀ = 3.8 μM) and stromelysin (IC₅₀ = 33 μM). Within this series of specifically claimed butyric acid derivatives, the following are also included:



Compound	R1	R2	A	Isomer	Formula
263763	Ac	H	O	S	C ₁₈ H ₁₅ NO ₅
263764	COCF3	H	O	S	C ₁₈ H ₁₂ F ₃ NO ₅
263765	COCF3	H	O	R	C ₁₈ H ₁₂ F ₃ NO ₅
264799	2,6-(i-Pr)2-PhNHCO	H	O	S	C ₂₉ H ₃₀ N ₂ O ₅
264800	SO2Me	H	O	S	C ₁₇ H ₁₅ NO ₆ S
264801	4-Me-PhSO2	H	O	S	C ₂₃ H ₁₉ NO ₆ S
264802	COCH=CHPh	H	O	S	C ₂₅ H ₁₉ NO ₅
264803	COPh	Me	O	S	C ₂₄ H ₁₉ NO ₅
264804	COCF3	H	N(OH)	S	C ₁₈ H ₁₃ F ₃ N ₂ O ₅



264805: C19-H14-F3-N-O4

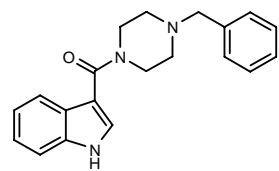
SOURCE – Warner-Lambert.

REFERENCES

1. Sliskovic, D.R. and Picard, J.A. (Warner-Lambert Co.) Butyric acid matrix metalloproteinase inhibitors. WO 9806711.

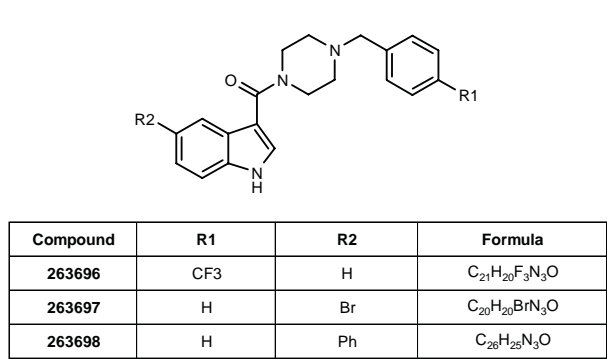
263258

1-Benzyl-4-(1H-indol-3-ylcarbonyl)piperazine



C20-H21-N3-O; Mol wt: 319.41

ACTION – An inhibitor of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF), as well as CSBP/p38/RK kinase activity. Potentially useful in the treatment of a broad range of conditions including rheumatoid arthritis, osteoarthritis, septic shock, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, psoriasis, restenosis, osteoporosis, graft-versus-host disease, transplant rejection and ulcerative colitis. Within this series of piperazine derivatives, the following are also included:



Certain compounds within the scope of the invention also inhibit cyclooxygenase type 2 (COX-2).

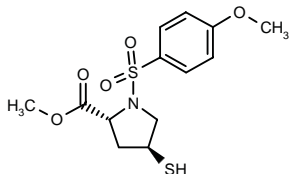
SOURCE – SmithKline Beecham.

REFERENCES

1. Adams, J.L. et al. (SmithKline Beecham Corp.; SmithKline Beecham plc) *Novel piperazine containing cpds.* WO 9806715.

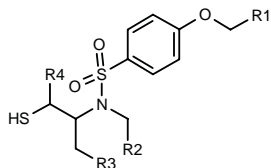
263338

1-(4-Methoxyphenylsulfonyl)-4(S)-sulfanylpyrrolidine-2(R)-carboxylic acid methyl ester



C13-H17-N-O5-S2; Mol wt: 331.40

ACTION – Agent for the treatment of osteoarthritis, periodontitis, corneal ulceration, tumor invasion and rheumatoid arthritis, an inhibitor of matrix metallo-proteinases. Within this series of bidentate compounds, the following are also included:



Compound	R1	R2,R3	R4	Isomer	Formula
264131	H	-CH(SH)-	H	4S,2R	C ₁₂ H ₁₇ NO ₃ S ₃
264132	H	-CH2-	H	2R	C ₁₂ H ₁₇ NO ₃ S ₂
264133	Pr	-(CH2)2-	H		C ₁₆ H ₂₅ NO ₃ S ₂
264134	H	-(CH2)2-	H		C ₁₃ H ₁₉ NO ₃ S ₂
264135	H	-(CH2)2-	2-thiazolyl		C ₁₆ H ₂₀ N ₂ O ₃ S ₃
264136	H	-(CH2)2-	CH2SH		C ₁₄ H ₂₁ NO ₃ S ₃

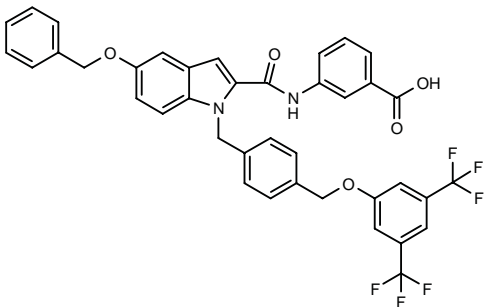
SOURCE – Procter & Gamble.

REFERENCES

1. Almstead, N.G. et al. (Procter & Gamble Co.) *Bidentate metalloprotease inhibitors.* WO 9808814.

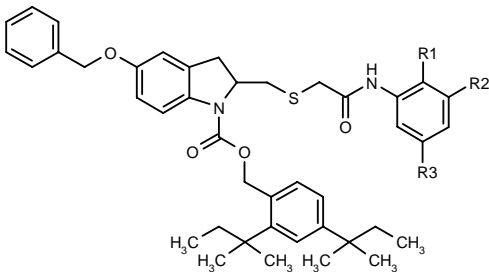
263342

3-[5-Benzyloxy-1-[4-[3,5-bis(trifluoromethyl)phenoxy-methyl]benzyl]indol-2-ylcarboxamido]benzoic acid

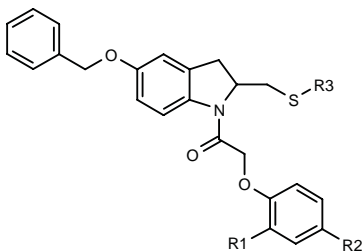


C39-H28-F6-N2-O5; Mol wt: 718.65

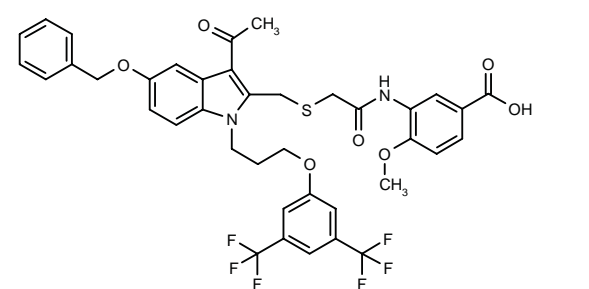
ACTION – Agent for the treatment of inflammatory disorders that acts via inhibition of phospholipase enzymes, particularly cytosolic phospholipase A₂ (IC₅₀ = 0.11 μM in the soluble substrate assay; IC₅₀ = 3.8 μM in the coumarin [PGE₂ production] assay). It proved active *in vivo* in the rat carrageenan-induced paw edema test (29% inhibition). Other related compounds include the following:



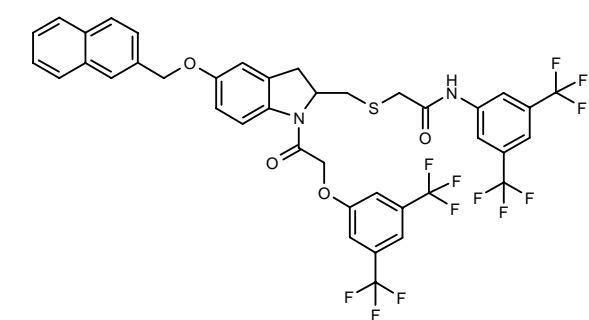
Compound	R1	R2	R3	Formula
264281	H	H	CO2H	C ₄₃ H ₅₀ N ₂ O ₅ S
264282	H	CO2H	CO2H	C ₄₄ H ₅₀ N ₂ O ₆ S
264283	OMe	H	CO2H	C ₄₄ H ₅₂ N ₂ O ₇ S
264284	OMe	H	CH(Me)CO2H	C ₄₆ H ₅₆ N ₂ O ₇ S
264285	OMe	H	CH(OMe)CO2H	C ₄₆ H ₅₆ N ₂ O ₈ S



Compound	R1	R2	R3	Formula
264287	H	CH2Ph	2-MeO-5-CO2H-PhNHCOCH2	C ₄₁ H ₃₈ N ₂ O ₇ S
264288	C(Me)2Et	C(Me)2Et	2-CO2H-Ph	C ₄₁ H ₄₇ NO ₅ S



264280: C39-H34-F6-N2-O7-S



264286: C40-H28-F12-N2-O4-S

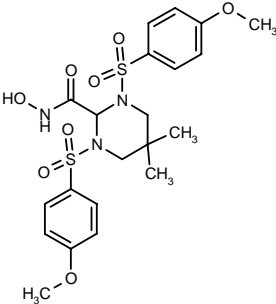
SOURCE – Genetics Inst.

REFERENCES

1. Xiang, Y. et al. (Genetics Inst., Inc.) *Inhibitors of phospholipase enzymes*. WO 9808818.

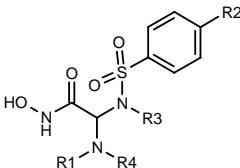
263345

1,3-Bis(4-methoxyphenylsulfonyl)-5,5-dimethylhexahydropyrimidine-2-carboxylic acid

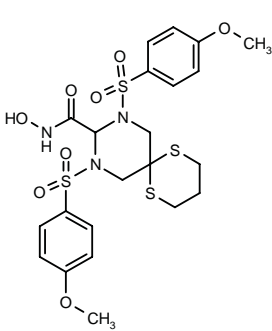


C21-H27-N3-O8-S2; Mol wt: 513.58

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, tumor metastasis and various ulcerative conditions that exerts its activity via inhibition of metalloproteinases such as collagenase, gelatinase and stromelysin. Within this series of 1,3-diheterocyclic compounds, the following are also included:



Compound	R1	R2	R3,R4	Formula
264295	4-MeO-PhSO2	OMe	-(CH2)2-	C ₁₈ H ₂₁ N ₃ O ₈ S ₂
264296	SO2Me	OMe	-(CH2)3-	C ₁₃ H ₁₉ N ₃ O ₇ S ₂
264297	Ac	OMe	-(CH2)3-	C ₁₄ H ₁₉ N ₃ O ₆ S
264299	CH2Ph	OMe	-CH2C(Me)2CO-	C ₂₁ H ₂₅ N ₃ O ₆ S
264300	CH2Ph	Br	-(CH2)3CO-	C ₁₉ H ₂₀ BrN ₃ O ₅ S



264298: C22-H27-N3-O8-S4

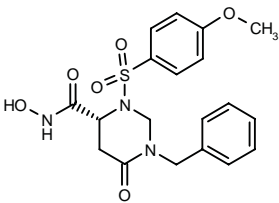
SOURCE – Procter & Gamble.

REFERENCES

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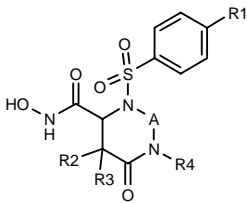
263346

1-Benzyl-3-(4-methoxyphenylsulfonyl)-6-oxohexahydro-pyrimidine-4(R)-carboxylic acid

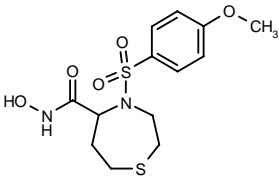


C19-H21-N3-O6-S; Mol wt: 419.45

ACTION – An inhibitor of matrix metalloproteinases claimed for use in the treatment of musculoskeletal disorders and cachexia. Other compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2=R3	R4	R5	Isomer	Formula
264553	OMe	H	-CH2-	Me	R	C ₁₃ H ₁₇ N ₃ O ₆ S
264554	OMe	Me	-CH2-	CH2Ph		C ₂₁ H ₂₅ N ₃ O ₆ S
264555	OMe	H	-(CH2)2-	i-Pr	R	C ₁₆ H ₂₃ N ₃ O ₆ S
264556	OMe	H	-(CH2)2-	CH2Ph	R	C ₂₀ H ₂₃ N ₃ O ₆ S
264558	NO2	Me	-(CH2)2-	i-Pr		C ₁₇ H ₂₄ N ₄ O ₇ S



264557: C13-H18-N2-O5-S2

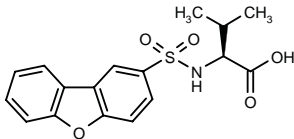
SOURCE – Procter & Gamble.

REFERENCES

1. Pikul, S. et al. (Procter & Gamble Co.) *Heterocyclic metalloprotease inhibitors*. WO 9808823.

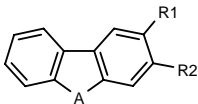
263793

N-(Dibenzofuran-2-ylsulfonyl)-L-valine



C17-H17-N-O5-S; Mol wt: 347.39

ACTION – Inibitor of matrix metalloproteinases (MMPs), particularly stromelysin 1 (MMP-3; IC₅₀ = 0.23 μM) and gelatinase A (MMP-2; IC₅₀ = 0.084 μM). Claimed for use in the treatment of multiple sclerosis, atherosclerosis, restenosis, aortic aneurysm, heart failure, periodontal disease, corneal ulceration, cancer metastasis, angiogenesis and arthritis. Within this series of tricyclic aromatic sulfonamide compounds, the following are aso included:



Compound	R1	R2	A	Formula
264695	SO2-L-Leu-OH	H	O	C ₁₈ H ₁₉ NO ₅ S
264696	H	SO2-L-Val-OH	O	C ₁₇ H ₁₇ NO ₅ S
264697	H	SO2-L-Val-OH	CH2	C ₁₈ H ₁₉ NO ₅ S

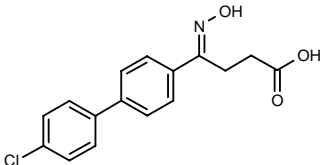
SOURCE – Warner-Lambert.

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1. O'Brien, P.M. et al. (Warner-Lambert Co.) *Matrix metalloproteinase inhibitors and their therapeutic uses*. WO 9809934.

263795

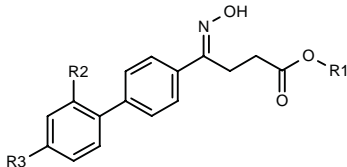
4-(4'-Chlorobiphenyl-4-yl)-4-(hydroxyimino)butyric acid



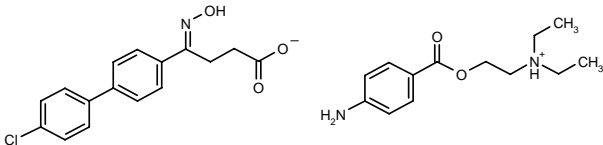
C16-H14-Cl-N-O3; Mol wt: 303.74

ACTION – Agent for the treatment of inflammation, immunological disorders and other conditions characterized by excess matrix metalloproteinase activity. In particular, the compound is a good inhibitor of gelatinase A (72-Kd gelatinase) and stromelysin 1 (IC₅₀ = 0.039 and 0.12 μM, respectively). *In vivo* in an experimental autoimmune encephalomyelitis (EAE) model in mice sensitized with a fragment of mouse myelin basic protein, compound at a dose of 50 mg/kg p.o. delayed the

onset of EAE, reduced the EAE cumulative score and prevented EAE-induced mortality. It was also active in a rat adjuvant arthritis model (99.9% inhibition of footpad edema at 30 mg/kg p.o. b.i.d. for 10 days) and against acetic acid-induced hyperalgesia in mice (ID₄₀ = 0.65 mg/kg p.o.). A particularly preferred compound within a series of specifically claimed biphenyl butyric acids, wherein the following are also included:



Compound	R1	R2	R3	Formula
265382	H	H	Br	C ₁₆ H ₁₄ BrNO ₃
265383	H	F	Br	C ₁₆ H ₁₃ BrFNO ₃
265384	H	F	Cl	C ₁₆ H ₁₃ ClFNO ₃
265385	H	H	OMe	C ₁₇ H ₁₇ NO ₄
265386	H	H	CN	C ₁₇ H ₁₄ N ₂ O ₃
265387	H	H	SMe	C ₁₇ H ₁₇ NO ₃ S
265388	Na	H	Cl	C ₁₆ H ₁₃ ClNaO ₃
265389	1/2Ca	H	Cl	C ₁₆ H ₁₃ CaClNO ₃



265390: C16-H14-Cl-N-O3.C13-H20-N2-O2

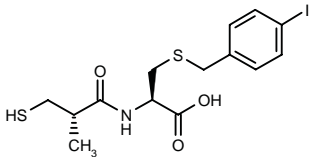
SOURCE – Warner-Lambert.

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1. Purchase, C.F. Jr. et al. (Warner-Lambert Co.) *Biphenyl butyric acids and their derivs. as inhibitors of matrix metalloproteinases*. WO 9809940.

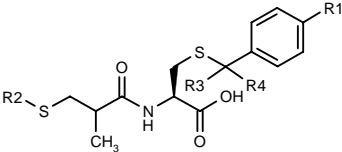
263796

S-(4-Iodobenzyl)-*N*-[2(*S*)-methyl-3-sulfanylpropionyl]-L-cysteine



C14-H18-I-N-O3-S2; Mol wt: 439.33

ACTION – Antiinflammatory agent for the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease and cystic fibrosis, a potent inhibitor of LTA₄ hydrolase (IC₅₀ = 15 nM in guinea pig lung preparations). Within this series of sulfur-containing amino acid derivatives, the following are also included:



Compound	R1	R2	R3	R4	Isomer	Formula
264776	t-Bu	COPh	H	H	S	C ₂₅ H ₃₁ NO ₄ S ₂
264777	I	COPh	H	H	S	C ₂₁ H ₂₂ INO ₄ S ₂
264778	Pr	H	H	H	S	C ₁₇ H ₂₅ NO ₃ S ₂
264779	t-Bu	H	H	H	S	C ₁₈ H ₂₇ NO ₃ S ₂
264780	t-Bu	H	H	H	RS	C ₁₈ H ₂₇ NO ₃ S ₂
264781	SMe	H	H	H	S	C ₁₅ H ₂₁ NO ₃ S ₃
264782	i-Pr	H	Me	H	S	C ₁₈ H ₂₇ NO ₃ S ₂
264783	i-Pr	H	Me	Me	S	C ₁₉ H ₂₉ NO ₃ S ₂
264784	i-Pr	H	Et	H	S	C ₁₉ H ₂₉ NO ₃ S ₂
264785	t-Bu	H	Me	H	R	C ₁₉ H ₂₉ NO ₃ S ₂
264786	cyclohexyl	H	H	H	S	C ₂₀ H ₂₉ NO ₃ S ₂
264787	cyclohexyl	H	Me	Me	S	C ₂₂ H ₃₃ NO ₃ S ₂

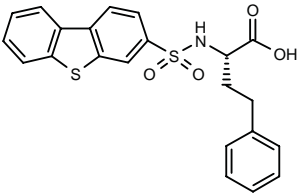
SOURCE – Santen.

REFERENCES

1. Horiuchi, M. et al. (Santen Pharm. Co., Ltd.) *Novel sulfur-containing amino acid derivs.* JP 98130225, WO 9809943.

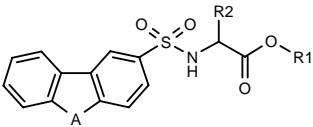
263801

2(S)-(Dibenzothiophen-3-ylsulfonamido)-4-phenylbutyric acid

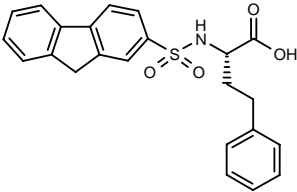


C22-H19-N-O4-S2; Mol wt: 425.52

ACTION – An inhibitor of matrix metalloproteinases, particularly gelatinase A (IC₅₀ = 0.0038 μM), stromelysin 1 (IC₅₀ = 0.013 μM) and collagenase 3 (IC₅₀ = 0.032 μM). Claimed for use in the treatment of multiple sclerosis, atherosclerosis, restenosis, aortic aneurysm, heart failure, periodontal disease, corneal ulceration, burns, decubital ulcers, chronic ulcers or wounds, cancer metastasis, tumor angiogenesis, arthritis and other autoimmune and inflammatory diseases dependent upon tissue invasion by leukocytes. Other related compounds include the following:



Compound	R1	R2	A	Formula
264978	H	(S)-CH ₂ CH ₂ Ph	O	C ₂₂ H ₁₉ NO ₅ S
264980	H	(CH ₂) ₄ NHCO ₂ CH ₂ Ph	O	C ₂₆ H ₂₆ N ₂ O ₇ S
264981	t-Bu	CH ₂ CH ₂ CO ₂ H	O	C ₂₁ H ₂₃ NO ₇ S
264982	H	CH ₂ CH ₂ CONHCH ₂ CH ₂ Ph	O	C ₂₅ H ₂₄ N ₂ O ₆ S
264983	H	4-Pr-PhCOCH ₂	O	C ₂₅ H ₂₃ NO ₆ S
264984	H	CH ₂ CH ₂ Ph	S	C ₂₂ H ₁₉ NO ₄ S ₂



264985: C23-H21-N-O4-S

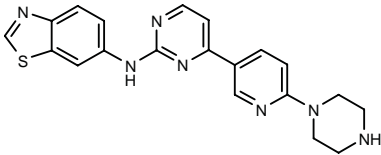
SOURCE – Warner-Lambert.

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1. Picard, J.A. and Sliskovic, D.R. (Warner-Lambert Co.) *Cpds. for and a method of inhibiting matrix metalloproteinases.* WO 9809957.

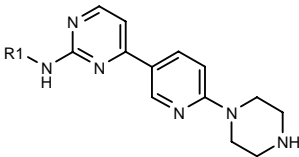
263851

N-(6-Benzothiazolyl)-N-[4-[6-(1-piperazinyl)pyridin-3-yl]pyrimidin-2-yl]amine



C20-H19-N7-S; Mol wt: 389.48

ACTION – Agent for the treatment or prevention of immune diseases such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, transplant rejection, graft-versus-host disease, hyperproliferative disorders such as cancer, psoriasis, restenosis and atherosclerosis, as well as asthma, inflammatory bowel disease and pancreatitis, an inhibitor of protein kinases, particularly the kinases p56^{lck} and ZAP-70 and protein kinase C. Other specifically claimed compounds from this series of substituted 2-pyrimidineamines include the following:



Compound	R1	Formula
265231	5-indazolyl	C ₂₀ H ₂₀ N ₈
265232	6-indazolyl	C ₂₀ H ₂₀ N ₈
265233	6-quinolyl	C ₂₂ H ₂₁ N ₇
265234	2-MeS-6-benzothiazolyl	C ₂₁ H ₂₁ N ₇ S ₂

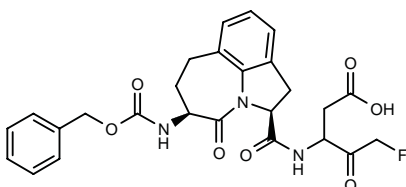
SOURCE – Celltech.

REFERENCES

1. Davis, P.D. et al. (Celltech Ther., Ltd.) *Substd. 2-pyrimidineamines, their preparation and their use as protein kinase inhibitors*. WO 9811095.

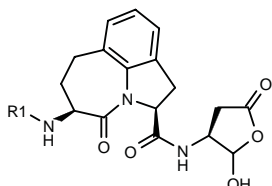
263861

3-[5(S)-(Benzyloxycarbonylamino)-4-oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*h*]indol-2(S)-ylcarboxamido]-5-fluoro-4-oxopentanoic acid



C26-H26-F-N3-O7; Mol wt: 511.51

ACTION – Agent for the treatment of inflammatory, autoimmune and neurodegenerative disorders, as well as for the prevention of ischemic injury, an irreversible inhibitor of IL-1 β -converting enzyme (ICE; K_i = 0.0005 μ M) and related cysteine proteases such as CPP32 (K_i = 0.012 μ M), MCH-2 (K_i = 0.033 μ M) and MCH-5 (K_i = 0.022 μ M). Other compounds from this series of tricyclic derivatives include the following:



Compound	R1	Formula
265191	CO ₂ CH ₂ Ph	C ₂₅ H ₂₅ N ₃ O ₇
265192	PhOCO-L-Asp-	C ₂₈ H ₂₈ N ₄ O ₁₀
265193	COCH ₂ CH ₂ Ph	C ₂₆ H ₂₇ N ₃ O ₆

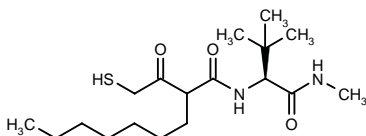
SOURCE – Idun.

REFERENCES

1. Karanewsky, D.S. and Linton, S.D. (Idun Pharm., Inc.) *Novel tricyclic cpds. for the inhibition of the ICE/ced-3 protease family of enzymes*. WO 9811109.

264487

N-[1(S)-[2,2-Dimethyl-1-(methylcarbamoyl)propyl]-2-(2-sulfanylacetyl)nonanamide



C18-H34-N2-O3-S; Mol wt: 358.54

ACTION – Matrix metalloproteinase (MMP) inhibitor proven active *in vitro* against collagenase 1 (MMP-1), stromelysin (MMP-3) and gelatinase B (MMP-9) (IC_{50} = 15, 16 and 0.3 nM, respectively). The most active compound from a series incorporating an alternative zinc ligand, potentially useful for the design of MMP inhibitors with improved bioavailability.

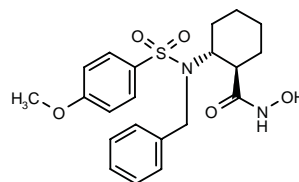
SOURCES – Affymax; Wyeth-Ayerst.

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2. Campbell, D.A. et al. (Affymax Technol. NV) *Novel inhibitors of metalloproteases, pharmaceutical compsns. comprising same and methods of their use*. WO 9640738.
3. Campbell, D.A. et al. *Malonyl α -mercaptoketones and α -mercaptoalcohols, a new class of matrix metalloproteinase inhibitors*. Bioorg Med Chem Lett 1998, 8(10): 1157.

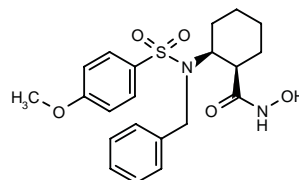
264837

trans-2-[*N*-Benzyl-*N*-(4-methoxyphenylsulfonyl)amino]-cyclohexanecarboxylic acid



C21-H26-N2-O5-S; Mol wt: 418.51

ACTION – An inhibitor of matrix metalloproteinases such as fibroblast collagenase (MMP-1; IC_{50} = 176 nM), gelatinase B (MMP-9; IC_{50} = 181 nM) and collagenase 3 (MMP-13; IC_{50} = 233 nM), as well as TNF- α -converting enzyme (TACE; IC_{50} = 1612 nM), with potential in the treatment of rheumatoid arthritis, tumor growth and metastasis, angiogenesis, bone disorders, inflammation, septic shock, congestive heart failure and HIV infection. Another specifically claimed compound from this series of β -sulfonamido hydroxamic acids is:



265644: C21-H26-N2-O5-S

SOURCE – American Cyanamid.

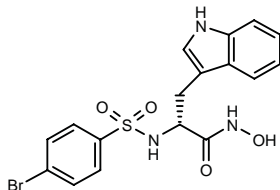
REFERENCES

1. Levin, J.I. et al. (American Cyanamid Co.) *β -Sulfonamido hydroxamic acids as matrix metalloproteinase and TACE inhibitors*. WO 9816506.

264874

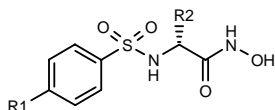
2(*R*)-(4-Bromophenylsulfonamido)-3-(3-indolyl)-propionohydroxamic acid

N^α-(4-Bromophenylsulfonyl)-*N*¹-hydroxy-D-tryptophanamide

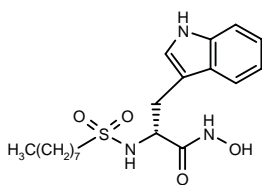


C17-H16-Br-N3-O4-S; Mol wt: 438.30

ACTION – An inhibitor of matrix metalloproteinases, especially gelatinase ($K_i = 0.0026 \mu\text{M}$), claimed for the treatment of diseases involving connective tissue degradation such as osteoarthritis and rheumatoid arthritis, as well as osteoporosis, tumor metastasis, periodontitis, gingivitis, corneal ulceration, dermal ulceration and gastric ulceration. Other specifically claimed compounds from this series of α -aminosulfonyl hydroxamic acids include the following:



Compound	R1	R2	Formula
265820	OMe	3-indolyl-CH2	C ₁₈ H ₁₉ N ₃ O ₅ S
265821	H	3-indolyl-CH2	C ₁₇ H ₁₇ N ₃ O ₄ S
265822	F	3-indolyl-CH2	C ₁₇ H ₁₆ FN ₃ O ₄ S
265823	OMe	CH2Ph	C ₁₆ H ₁₈ N ₂ O ₅ S
265825	OMe	Ph	C ₁₅ H ₁₆ N ₂ O ₅ S
265826	OMe	i-Pr	C ₁₂ H ₁₈ N ₂ O ₅ S
265827	H	i-Pr	C ₁₁ H ₁₆ N ₂ O ₄ S
265828	OMe	C(Me) ₂ Et	C ₁₄ H ₂₂ N ₂ O ₅ S



265824: C19-H29-N3-O4-S

SOURCE – Pharmacia & Upjohn.

REFERENCES

- Warpehoski, M.A. et al. (Pharmacia & Upjohn Co.) α -Amino sulfonyl hydroxamic acids as matrix metalloproteinase inhibitors. WO 9817645.

INTERLEUKIN-19

263369

IL-19

ACTION – Human cytokine with significant homology to IL-10 that is expressed primarily in activated monocytes and is useful for inhibiting the production of cytokines such as interferon gamma, tumor necrosis factor- α (TNF- α) and IL-6. Potentially useful in the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, insulin-dependent diabetes mellitus and thyroiditis, as well as for counteracting the side effects of adoptive immunotherapy. Also provided are vectors, host cells and recombinant methods for producing the polypeptide. Additionally, antagonists including antibodies are provided, which may be used to increase IL-2 activity and thus restore immune function in HIV-infected patients.

SOURCE – Human Genome Sciences.

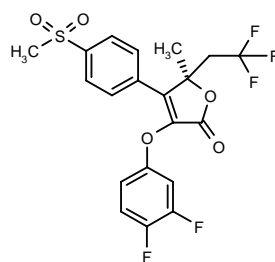
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- Rosen, C.A. and Kenny, J.J. (Human Genome Sci., Inc.) *Interleukin-19*. WO 9808870.

L-784512

265846

3-(3,4-Difluorophenoxy)-5(*R*)-methyl-4-[4-(methylsulfonyl)phenyl]-5-(2,2,2-trifluoroethyl)furan-2(5*H*)-one



C20-H15-F5-O5-S; Mol wt: 462.39

ACTION – Antiinflammatory agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated using purified recombinant human COX-2, transfected CHO cells expressing human COX-2 and against lipopolysaccharide (LPS)-induced PGE₂ formation in human whole blood (IC₅₀ = 3.0, 0.05 and 1.1 μM , respectively), with good selectivity over COX-1 (IC₅₀ = 29 μM in CHO cells expressing human COX-1). Compound inhibited carrageenan-induced rat paw edema with an ED₅₀ of 1.0 mg/kg p.o.

SOURCE – Merck & Co.

REFERENCES

- Belley, M. et al. (Merck Frosst Canada, Inc.) (Methylsulfonyl)phenyl-2-(5*H*)-furanones as COX-2 inhibitors. WO 9714691.
- Black, C. et al. (Merck Frosst Canada, Inc.) 3,4-Diaryl-2-hydroxy-2,5-dihydrofurans as prodrugs to COX-2 inhibitors. US 5698584, WO 9716435.
- Tan, L. et al. An efficient asymmetric synthesis of a potent COX-2 inhibitor L-784,512. Tetrahedron Lett 1998, 39(23): 3961.

MCP-3 (9-76)

263267

ACTION – Agent for the treatment of inflammatory and autoimmune disorders, an NH₂-terminally truncated analog of human monocyte chemoattractant protein-3 (MCP-3) with antagonist activity against MCP-3. Compound (3 mg/kg/day i.p. x 30 days) inhibited swelling and reduced the incidence of arthritis in an adjuvant-induced arthritis model in mice and it was not toxic. Other truncated analogs of human chemokines (RANTES [Regulated on Activation, Normal T-cell Expressed and Secreted] and MIP-1α [macrophage inflammatory protein-1α]) include the following:

MIP-α(10-70) [264039]

RANTES(9-68) [264040]

SOURCE – Research Corporation Technologies.

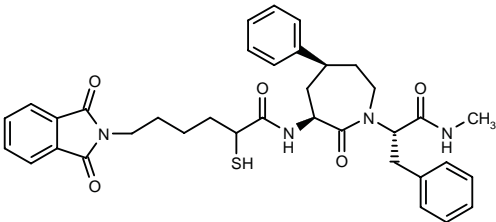
REFERENCES

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MDL-108180

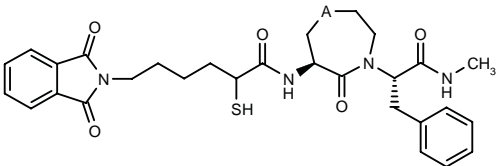
263892

[3S-[1(1*R**),3α,5α]]-6-(1,3-Dioxoisindolin-2-yl)-*N*-[1-[1-(*N*-methylcarbamoyl)-2-phenylethyl]-2-oxo-5-phenylperhydroazepin-3-yl]-2-sulfanylhexanamide



C36-H40-N4-O5-S; Mol wt: 640.80

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, chronic inflammatory disorders such as emphysema or chronic bronchitis, cardiovascular disorders such as atherosclerosis, corneal ulceration, gingivitis, periodontal disease, cancer and neurological disorders such as multiple sclerosis, an inhibitor of matrix metalloproteinases (MMPs) such as gelatinase A (MMP-2; K_i = 1.2 nM), stromelysin 1 (MMP-3; K_i = 39 nM) and metalloelastase (MMP-12; K_i = 18 nM). Other compounds from this series of 3-mercaptoacetyl-amino-2-oxoazepan derivatives include the following:



Compound	A	Formula
MDL-106540 [265229]	(<i>R</i>)-CH(Ph)	C ₃₆ H ₄₀ N ₄ O ₅ S
265230	-N(CH ₂ Ph)-	C ₃₆ H ₄₁ N ₅ O ₅ S

SOURCE – Hoechst Marion Roussel.

REFERENCES

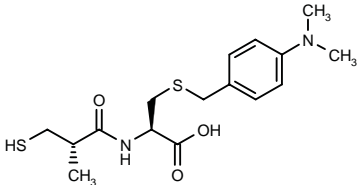
1. Warshawsky, A.M. et al. (Hoechst Marion Roussel, Inc.) 3-Mercaptoacetyl-amino-1,5-substd.-2-oxo-azepan derivs. useful as inhibitors of matrix metalloproteinase. WO 9812211.

SA-6541*

241773

3-[4-(Dimethylamino)benzylsulfanyl]-2(*R*)-[2(*S*)-methyl-3-sulfanylpropionamido]propionic acid

S-[4-(Dimethylamino)benzyl]-*N*-[2(*S*)-methyl-3-sulfanylpropionyl]-L-cysteine



C16-H24-N2-O3-S2; Mol wt: 356.50

ACTION – Antiinflammatory agent, an LTA₄ hydrolase inhibitor that prevents the synthesis of LTB₄. In a model of carrageenan-induced mouse ear edema, compound at 100 mg/kg p.o. inhibited edema formation by 20% at 4 h and neutrophil accumulation by 53% at 8 h after carrageenan injection. It also inhibited the increase in LTB₄ at 30 min by 73%, but had no effect on the increase in PGE₂. Its effects on edema formation were potentiated when used in combination with the PGE₂ formation inhibitor indomethacin (48% inhibition).

SOURCE – Santen.

REFERENCES

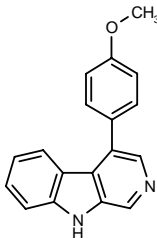
1. Kawashima, Y. and Horiuchi, M. (Santen Pharm. Co., Ltd.) Novel amino acid derivs. having *N,N*-dialkylaminophenyl group. JP 96301840, WO 9627585.
2. Tsuji, F. et al. Effects of SA6541, a leukotriene A₄ hydrolase inhibitor, and indomethacin on carrageenan-induced murine dermatitis. Eur J Pharmacol 1998, 346(1): 81.
3. Tsuji, F. et al. Involvement of leukotriene B₄ in murine dermatitis model. Biochem Pharmacol 1998, 55: 297.

*Identified compound 241773 Drug Data Rep 1997, 19(2): 157.

IMMUNOLOGIC DRUGS

263260

4-(4-Methoxyphenyl)-9*H*-pyrido[3,4-*b*]indole



C18-H14-N2-O; Mol wt: 274.32

MCP-3 (9-76)

263267

ACTION – Agent for the treatment of inflammatory and autoimmune disorders, an NH₂-terminally truncated analog of human monocyte chemoattractant protein-3 (MCP-3) with antagonist activity against MCP-3. Compound (3 mg/kg/day i.p. x 30 days) inhibited swelling and reduced the incidence of arthritis in an adjuvant-induced arthritis model in mice and it was not toxic. Other truncated analogs of human chemokines (RANTES [Regulated on Activation, Normal T-cell Expressed and Secreted] and MIP-1 α [macrophage inflammatory protein-1 α]) include the following:

MIP- α (10-70) [264039]**RANTES(9-68) [264040]****SOURCE** – Research Corporation Technologies.

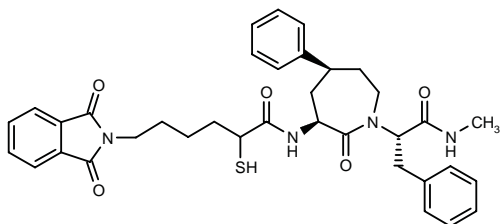
REFERENCES

1. Clark-Lewis, I. and Gong, J.-H. (Research Corp. Technol., Inc.) MCP-3, RANTES and MIP-1 α receptor antagonists. WO 9806751.

MDL-108180

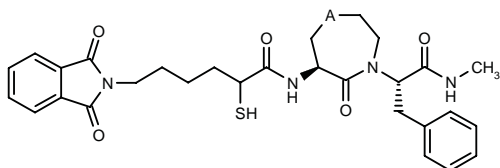
263892

[3S-[1(1*R**),3 α ,5 α]]-6-(1,3-Dioxoisindolin-2-yl)-N-[1-[1-(*N*-methylcarbamoyl)-2-phenylethyl]-2-oxo-5-phenylperhydroazepin-3-yl]-2-sulfanylhexasamide



C36-H40-N4-O5-S; Mol wt: 640.80

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, chronic inflammatory disorders such as emphysema or chronic bronchitis, cardiovascular disorders such as atherosclerosis, corneal ulceration, gingivitis, periodontal disease, cancer and neurological disorders such as multiple sclerosis, an inhibitor of matrix metalloproteinases (MMPs) such as gelatinase A (MMP-2; K_i = 1.2 nM), stromelysin 1 (MMP-3; K_i = 39 nM) and metalloelastase (MMP-12; K_i = 18 nM). Other compounds from this series of 3-mercaptoacetyl-amino-2-oxoazepan derivatives include the following:



Compound	A	Formula
MDL-106540 [265229]	(R)-CH(Ph)	C ₃₆ H ₄₀ N ₄ O ₅ S
265230	-N(CH ₂ Ph)-	C ₃₆ H ₄₁ N ₅ O ₅ S

SOURCE – Hoechst Marion Roussel.

REFERENCES

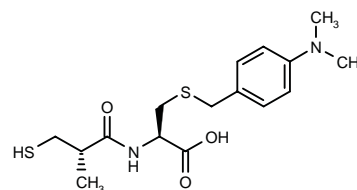
1. Warshawsky, A.M. et al. (Hoechst Marion Roussel, Inc.) 3-Mercaptoacetyl-amino-1,5-substd.-2-oxo-azepan derivs. useful as inhibitors of matrix metalloproteinase. WO 9812211.

SA-6541*

241773

3-[4-(Dimethylamino)benzylsulfanyl]-2(*R*)-[2(*S*)-methyl-3-sulfanylpropionamido]propionic acid

S-[4-(Dimethylamino)benzyl]-N-[2(*S*)-methyl-3-sulfanylpropionyl]-L-cysteine



C16-H24-N2-O3-S2; Mol wt: 356.50

ACTION – Antiinflammatory agent, an LTA₄ hydrolase inhibitor that prevents the synthesis of LTB₄. In a model of carrageenan-induced mouse ear edema, compound at 100 mg/kg p.o. inhibited edema formation by 20% at 4 h and neutrophil accumulation by 53% at 8 h after carrageenan injection. It also inhibited the increase in LTB₄ at 30 min by 73%, but had no effect on the increase in PGE₂. Its effects on edema formation were potentiated when used in combination with the PGE₂ formation inhibitor indomethacin (48% inhibition).

SOURCE – Santen.

REFERENCES

1. Kawashima, Y. and Horiuchi, M. (Santen Pharm. Co., Ltd.) Novel amino acid derivs. having N,N-dialkylaminophenyl group. JP 96301840, WO 9627585.

2. Tsuji, F. et al. Effects of SA6541, a leukotriene A₄ hydrolase inhibitor, and indomethacin on carrageenan-induced murine dermatitis. Eur J Pharmacol 1998, 346(1): 81.

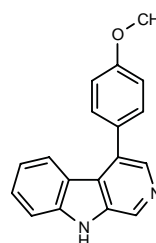
3. Tsuji, F. et al. Involvement of leukotriene B₄ in murine dermatitis model. Biochem Pharmacol 1998, 55: 297.

*Identified compound **241773** Drug Data Rep 1997, 19(2): 157.

IMMUNOLOGIC DRUGS

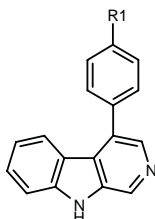
263260

4-(4-Methoxyphenyl)-9*H*-pyrido[3,4-*b*]indole



C18-H14-N2-O; Mol wt: 274.32

ACTION – Immunomodulator that inhibits Ca^{2+} influx and IL-2 production. The IC_{50} for inhibiting calcium influx in thapsigargin-stimulated Jurkat cells (clone E6-1) was 0.3 μM , and IC_{50} values for inhibiting IL-2 production in mononuclear cell fractions of human peripheral blood stimulated by ionomycin and PMA or by anti-CD3/anti-CD28 were 1 and 4.2 μM , respectively. Compound was assessed *in vivo* by measuring its ability to inhibit the allogeneic cell transplant response in mice, giving 60% inhibition at 1 mg/kg p.o. In addition, it also inhibited transcriptional activation of a luciferase reporter gene (IL-2 promoter assay) with an IC_{50} of 1.09 μM . Other specifically claimed 4-substituted β -carboline include the following:



Compound	R1	Formula
263687	CF ₃	C ₁₈ H ₁₁ F ₃ N ₂
263688	i-Pr	C ₂₀ H ₁₈ N ₂
263689	N(Me) ₂	C ₁₉ H ₁₇ N ₃
264794	Me	C ₁₈ H ₁₄ N ₂

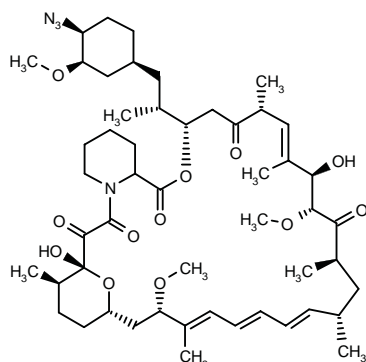
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Hargrave, K.D. et al. (Boehringer Ingelheim Pharm., Inc.) 4-Subst. β -carboline as immunomodulators. WO 9806719.

263810

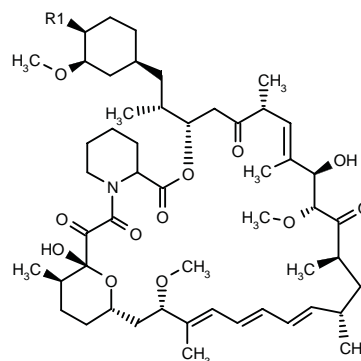
[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*S*)]15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*]-12-[2-(4-Azido-3-methoxycyclohexyl)-1-methylethyl]-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone



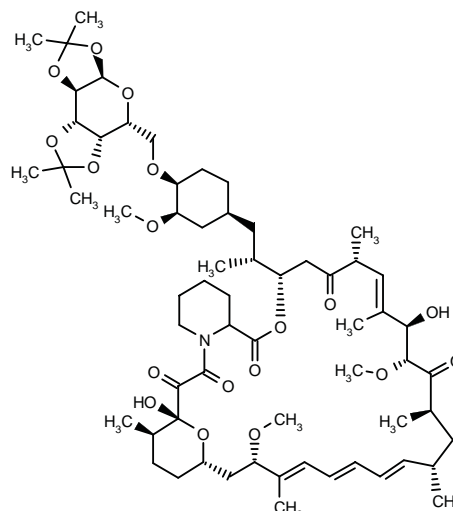
C51-H78-N4-O12; Mol wt: 939.20

ACTION – Immunosuppressant, also reported to possess antiinflammatory, antitumor and antifungal activity. *In vitro*, compound inhibited mitogen-induced murine thymocyte proliferation (IC_{50} = 1.70 nM; IC_{50} rapamycin/ IC_{50} test compound = 0.24). It prolonged survival time of pinch skin grafts from male DBA/2 donors transplanted to male BALB/c recipients following i.p. administration and was

active against adjuvant-induced arthritis in rats following oral administration. In addition, compound is reported to inhibit the proliferation of prostate PC-3 and DU-145, breast T47D and SKBR-3, colon MIP 101 and ovarian A27805 tumor cells. Other compounds from this series of rapamycin (sirolimus) derivatives include the following:



Compound	R1	Formula
265159	-SCN	C ₅₂ H ₇₈ N ₂ O ₁₂ S
265161	NHAc	C ₅₃ H ₈₂ N ₂ O ₁₃
265162	-NHCN	C ₅₂ H ₇₉ N ₃ O ₁₂
265163	4,5-(CO ₂ Me)-1,2,3-triazol-1-yl	C ₅₇ H ₈₄ N ₄ O ₁₆



265160: C63-H97-N-O18

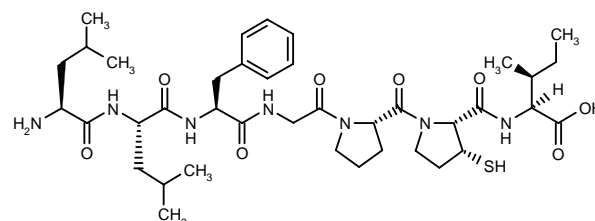
SOURCE – American Home Products.

REFERENCES

1. Grinfield, A.A. et al. (American Home Prods. Corp.) Rapamycin derivs. with unnatural stereochemistries. WO 9809972.

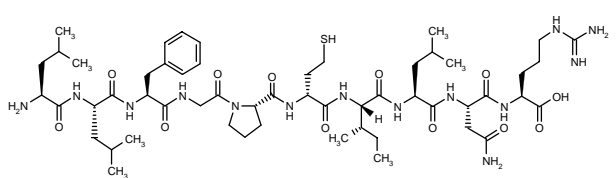
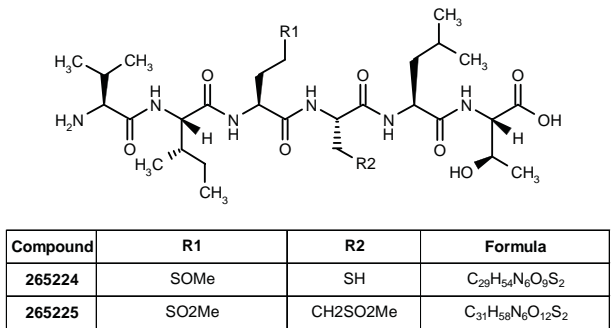
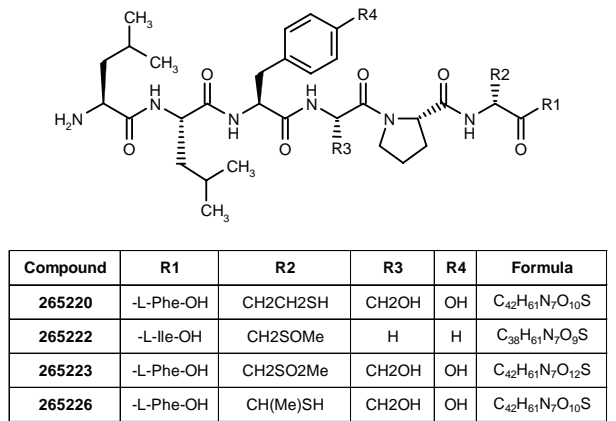
263893

Leucyl-leucyl-phenylalanyl-glycyl-prolyl-[3(*R*)-sulfanyl]-prolyl-isoleucine

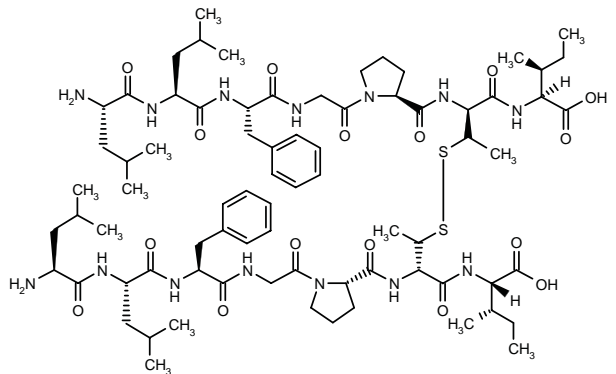


C39-H61-N7-O8-S; Mol wt: 788.01

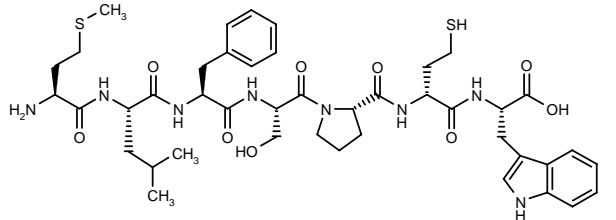
ACTION – Orally active immunomodulatory peptide that is absorbed through the epithelial cell lining of the gut following oral administration; compound is believed to act via interaction with mucosal associated lymphoid tissue (MALT). Claimed for the treatment of cancer, rheumatoid arthritis and autoimmune diseases. Other specifically claimed peptides include the following:



265221: C54-H90-N14-O12-S



265227: C76-H120-N14-O16-S2



265228: C43-H60-N8-O9-S2

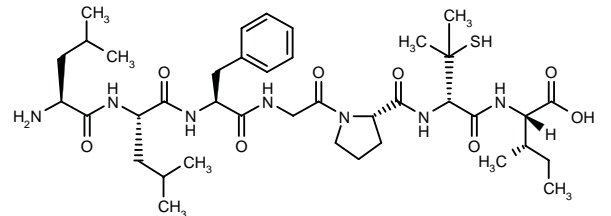
SOURCE – Astra.

REFERENCES

1. Bergstrand, H. et al. (Astra AB) Cysteine analogue containing peptides having immunomodulatory effect. WO 9812214.

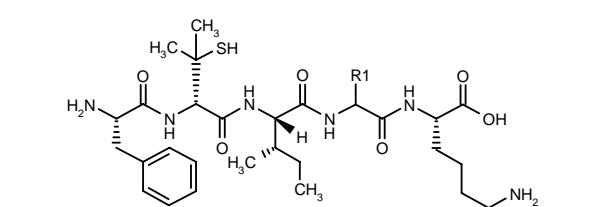
263894

Leucyl-leucyl-phenylalanyl-glycyl-prolyl-penicillaminyl-isoleucine

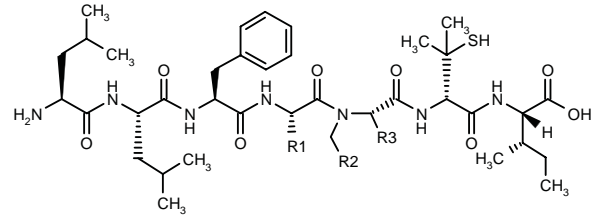


C39-H63-N7-O8-S; Mol wt: 790.03

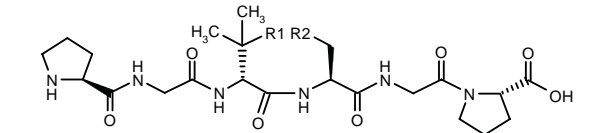
ACTION – Orally active immunomodulatory peptide that is absorbed through the epithelial cell lining of the gut following oral administration; compound is believed to act via interaction with mucosal associated lymphoid tissue (MALT). Claimed for the treatment of cancer, rheumatoid arthritis and autoimmune diseases. Within this series of penicillamine-containing peptides, the following are also specifically claimed:



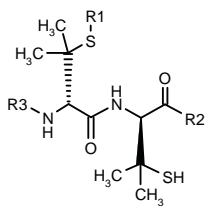
Compound	R1	Formula
265608	(R)-CH2SH	C ₂₉ H ₄₈ N ₆ O ₆ S ₂
265609	(S)-C(Me)2SH	C ₃₁ H ₅₂ N ₆ O ₆ S ₂



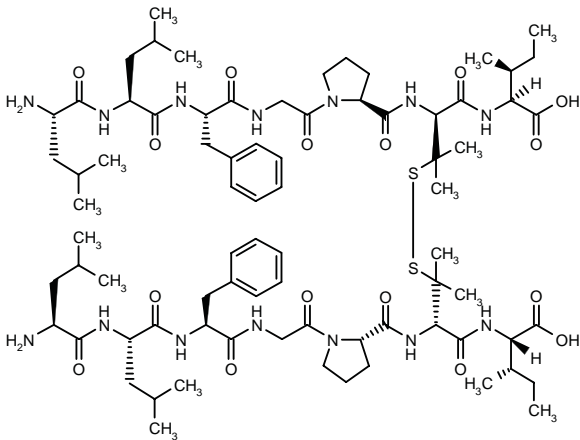
Compound	R1	R2,R3	Formula
265610	CH2CO2H	-(CH2)2-	C ₄₁ H ₆₈ N ₇ O ₁₀ S
265611	(CH2)3NHC(=NH)NH2	-(CH2)2-	C ₄₃ H ₇₂ N ₁₀ O ₈ S
265612	H	-(CH2)3-	C ₄₀ H ₆₅ N ₇ O ₈ S



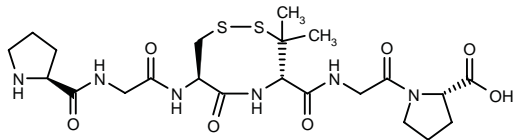
Compound	R1	R2	Formula
265615	-S-S-		C ₂₂ H ₃₄ N ₆ O ₇ S ₂
265617	SH	SH	C ₂₂ H ₃₆ N ₆ O ₇ S ₂



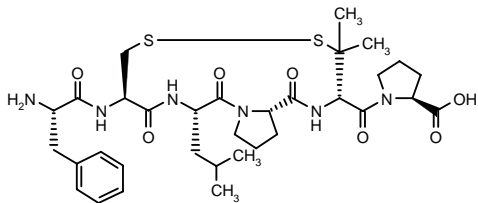
Compound	R1	R2	R3	Formula
265618	H	-Gly-L-Pro-OH	H-L-Pro-Gly-	C ₂₄ H ₄₀ N ₆ O ₇ S ₂
265620	H	-L-Leu-L-Thr-OH	H-L-Val-L-Ile-	C ₃₁ H ₅₈ N ₆ O ₈ S ₂
265621	CH ₂ NHAc	-Gly-L-Pro-OH	H-L-Pro-Gly-	C ₂₇ H ₄₅ N ₇ O ₈ S ₂



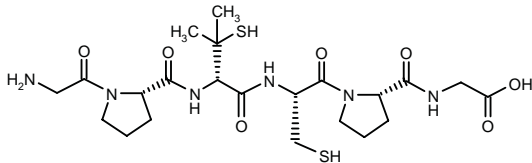
265613: C78-H124-N14-O16-S2



265614: C22-H34-N6-O7-S2



265616: C33-H48-N6-O7-S2



265619: C22-H36-N6-O7-S2

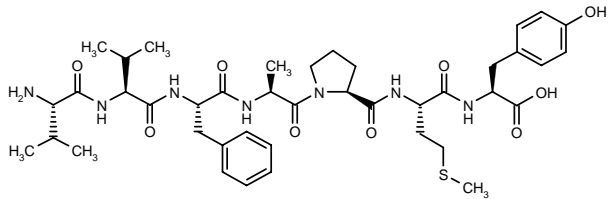
SOURCE – Astra.

REFERENCES

1. Bergstrand, H. et al. (Astra AB) *Penicillamine containing peptides having immunomodulatory effect.* WO 9812215.

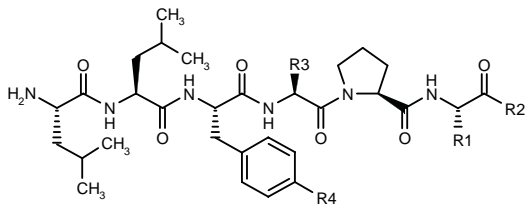
263898

Valyl-valyl-phenylalanyl-alanyl-prolyl-methionyl-tyrosine

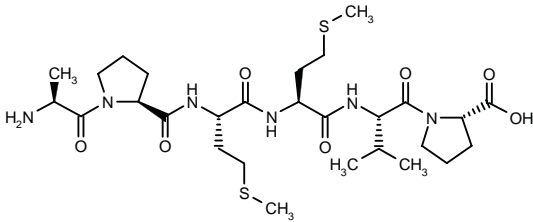


C41-H59-N7-O9-S; Mol wt: 826.02

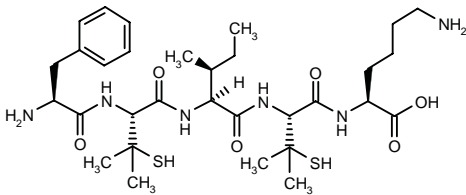
ACTION – Orally active immunomodulatory peptide that is absorbable by the epithelial cell lining, thus resulting in a modulated immune response; compound is believed to act via interaction with mucosal associated lymphoid tissue (MALT). Claimed for the treatment of cancer, rheumatoid arthritis and autoimmune diseases. Other specifically claimed peptides include the following:



Compound	R1	R2	R3	R4	Formula
265622	CH ₂ CH ₂ SMMe	-L-Phe-OH	CH ₂ OH	OH	C ₄₃ H ₆₃ N ₇ O ₁₀ S
265624	CH ₂ CH ₂ SMMe	-L-Ile-OH	CH ₂ CO ₂ H	H	C ₄₁ H ₆₅ N ₇ O ₁₀ S
265625	C(Me) ₂ SH	-L-Ile-OH	H	H	C ₃₉ H ₆₃ N ₇ O ₈ S



265623: C28-H48-N6-O7-S2



265626: C31-H52-N6-O6-S2

SOURCE – Astra.

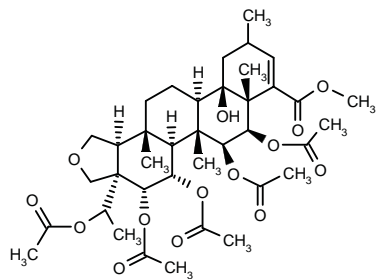
REFERENCES

1. Bergstrand, H. et al. (Astra AB) *Methionine containing peptides having immunomodulatory effect.* WO 9812216.

2. Bergstrand, H. et al. (Astra AB) *Methionine, penicillamine and cysteine-analogue containing peptides having immunomodulating activity.* WO 9812219.

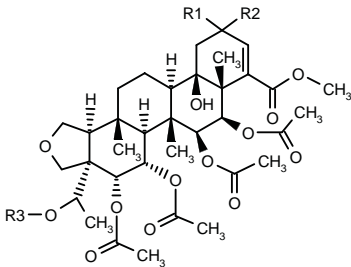
264841

[3a*R*-(3aα,4α,5α,5aα,6bβ,6β,7β,7aβ,11aβ,11bα,13aβ,13bα)]-4,5,6,7-Tetraacetoxy-3a-(1-acetoxyethyl)-11a-hydroxy-5b,7a,10,13a-tetramethyl-1,3,3a,4,5,5a,5b,6,7,7a,10,11,11a,11b,12,13,13a,13b-octadecahydrochryseno[1,2-*c*]furan-8-carboxylic acid methyl ester

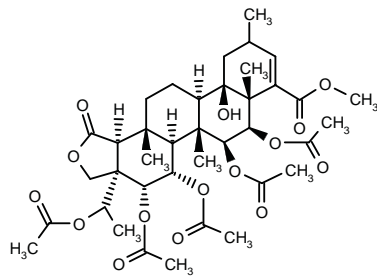


C38-H54-O14; Mol wt: 734.83

ACTION – Immunosuppressant for the treatment of autoimmune diseases and the prevention of organ rejection that acts by inhibiting voltage-gated Kv 1.3 potassium channels found in human T-lymphocytes. Other specifically claimed compounds from this series of triterpene derivatives include the following:



Compound	R1	R2	R3	Formula
265939	Me	H	H	C ₃₆ H ₅₂ O ₁₃
265940	Me	H	2-Br-PhCO	C ₄₃ H ₅₅ BrO ₁₄
265942	-O-		Ac	C ₃₇ H ₅₀ O ₁₅
265943	OCH2OMe	H	Ac	C ₃₉ H ₅₆ O ₁₆
265944	OCH2OEt	H	Ac	C ₄₀ H ₅₈ O ₁₆



265941: C38-H52-O15

SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Triterpene derivs. with immunosuppressant activity*. WO 9816518.

CHEMOKINE ALPHA-4

263864

CKα-4

ACTION – Human polypeptide belonging to the CXC chemokine family with potential as an antiinflammatory, angiostatic and antineovascularizing agent, as well as for the treatment of immune and autoimmune diseases, to stimulate wound healing, to regulate hematopoiesis and for the treatment of sepsis. Nucleotides encoding this polypeptide, as well as vectors, host cells and recombinant methods for preparing the same, are provided. Also disclosed are screening methods for identifying agonists and antagonists of this peptide, as well as diagnostic methods for detecting immune system-related disorders.

SOURCE – Human Genome Sciences.

REFERENCES

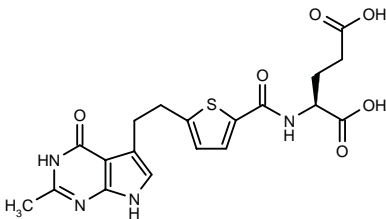
1. Olsen, H.S. et al. (Human Genome Sci., Inc.) *Chemokine alpha-4*. WO 9811138.

ONCOLYTIC DRUGS

ANTIMETABOLITES

263316

N-[5-[2-(2-Methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]thien-2-ylcarbonyl]-L-glutamic acid

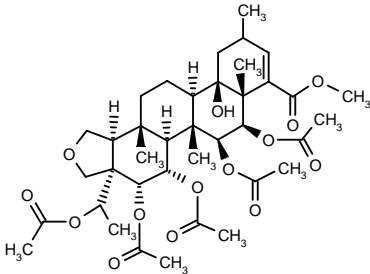


C19-H20-N4-O6-S; Mol wt: 432.45

ACTION – A nonclassical, nonpolyglutamatable antifolate shown to inhibit human thymidylate synthase with a *K_i* value of 455 nM and to potently inhibit the growth of human colon carcinoma GC3 cells in an MTT assay (IC₅₀ = 0.24 μg/ml). Claimed for use in the treatment of tumors, arthritis and psoriasis. Within this series of specifically claimed pyrrolo[2,3-*d*]pyrimidines, the following are also included:

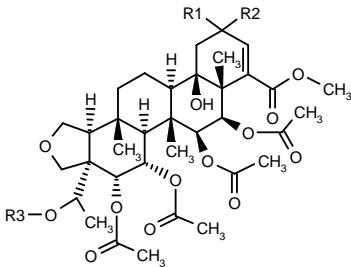
264841

[3a*R*-(3aα,4α,5α,5aα,6bβ,6β,7β,7aβ,11aβ,11bα,13aβ,13bα)]-4,5,6,7-Tetraacetoxy-3a-(1-acetoxyethyl)-11a-hydroxy-5b,7a,10,13a-tetramethyl-1,3,3a,4,5,5a,5b,6,7,7a,10,11,11a,11b,12,13,13a,13b-octadecahydrochryseno[1,2-*c*]furan-8-carboxylic acid methyl ester

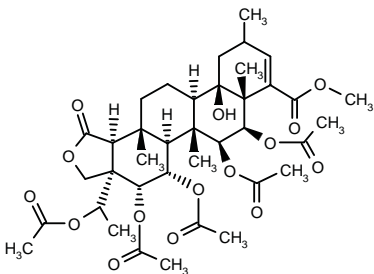


C38-H54-O14; Mol wt: 734.83

ACTION – Immunosuppressant for the treatment of autoimmune diseases and the prevention of organ rejection that acts by inhibiting voltage-gated Kv 1.3 potassium channels found in human T-lymphocytes. Other specifically claimed compounds from this series of triterpene derivatives include the following:



Compound	R1	R2	R3	Formula
265939	Me	H	H	C ₃₆ H ₅₂ O ₁₃
265940	Me	H	2-Br-PhCO	C ₄₃ H ₅₅ BrO ₁₄
265942	-O-		Ac	C ₃₇ H ₅₀ O ₁₅
265943	OCH2OMe	H	Ac	C ₃₉ H ₅₆ O ₁₆
265944	OCH2OEt	H	Ac	C ₄₀ H ₅₈ O ₁₆



265941: C38-H52-O15

SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Triterpene derivs. with immunosuppressant activity*. WO 9816518.

CHEMOKINE ALPHA-4

263864

CKα-4

ACTION – Human polypeptide belonging to the CXC chemokine family with potential as an antiinflammatory, angiostatic and antineovascularizing agent, as well as for the treatment of immune and autoimmune diseases, to stimulate wound healing, to regulate hematopoiesis and for the treatment of sepsis. Nucleotides encoding this polypeptide, as well as vectors, host cells and recombinant methods for preparing the same, are provided. Also disclosed are screening methods for identifying agonists and antagonists of this peptide, as well as diagnostic methods for detecting immune system-related disorders.

SOURCE – Human Genome Sciences.

REFERENCES

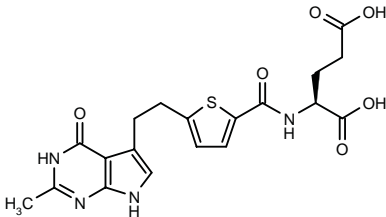
1. Olsen, H.S. et al. (Human Genome Sci., Inc.) *Chemokine alpha-4*. WO 9811138.

ONCOLYTIC DRUGS

ANTIMETABOLITES

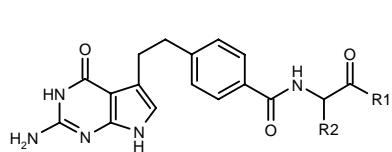
263316

N-[5-[2-(2-Methyl-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]thien-2-ylcarbonyl]-L-glutamic acid

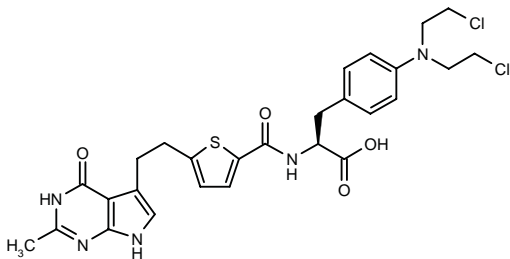


C19-H20-N4-O6-S; Mol wt: 432.45

ACTION – A nonclassical, nonpolyglutamatable antifolate shown to inhibit human thymidylate synthase with a *K_i* value of 455 nM and to potently inhibit the growth of human colon carcinoma GC3 cells in an MTT assay (IC₅₀ = 0.24 μg/ml). Claimed for use in the treatment of tumors, arthritis and psoriasis. Within this series of specifically claimed pyrrolo[2,3-*d*]pyrimidines, the following are also included:



Compound	R1	R2	Isomer	Formula
264450	OH	4-CO2H-PhSO2-NHCOCH2CH2	S	C ₂₇ H ₂₆ N ₆ O ₉ S
264451	OH	3-CO2H-PhSO2-NHCOCH2CH2	S	C ₂₇ H ₂₆ N ₆ O ₉ S
264452	OH	CH2CH2CO-NHSO2Me	S	C ₂₁ H ₂₄ N ₆ O ₇ S
264453	OH	CH(Me)CH2CO2H	S	C ₂₁ H ₂₃ N ₆ O ₆
264454	OCH2Ph	CH2CH2CO2H	S	C ₂₇ H ₂₇ N ₆ O ₆
264455	OH	CH2CH2CO2CH2Ph	S	C ₂₇ H ₂₇ N ₆ O ₆
264456	-L-Val-OH	CH2CH2CO2H	S	C ₂₅ H ₃₀ N ₆ O ₇
264457	OH	4-Cl-PhCH2	R,S	C ₂₄ H ₂₂ ClN ₆ O ₄
264459	NH2	CH2CH2CO2H	S	C ₂₀ H ₂₂ N ₆ O ₅



264458: C27-H29-Cl2-N5-O4-S

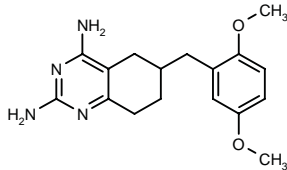
SOURCE – Lilly.

REFERENCES

1. Jordan, C.L. et al. (Eli Lilly & Co.) *Nonclassical pyrrolo[2,3-d]pyrimidine antifolates*. WO 9808382.

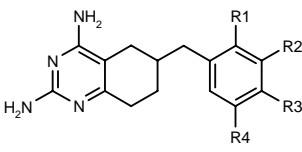
264789

6-(2,5-Dimethoxybenzyl)-5,6,7,8-tetrahydroquinazoline-2,4-diamine



C17-H22-N4-O2; Mol wt: 314.39

ACTION – Antineoplastic and antiparasitic agent, a potent inhibitor of dihydrofolate reductase (DHFR) that inhibits mammalian DHFR with an IC₅₀ in the range of 30-60 nM, and also the bifunctional *Toxoplasma gondii* DHFR-TS (IC₅₀ = 20-25 nM). *In vitro* activity was studied against the NCI panel of 60 cell lines, giving an IC₅₀ of < 10 nM in 21%, 10-100 nM in 18%, 100-1000 nM in 22%, and > 1000 nM in 38% of cell lines. Other compounds from this series of piritrexim and trimetrexate analogs include the following:



Compound	R1	R2	R3	R4	Formula
264790	OMe	H	H	H	C ₁₆ H ₂₀ N ₄ O
264791	H	OMe	OMe	H	C ₁₇ H ₂₂ N ₄ O ₂
264792	H	OMe	OMe	OMe	C ₁₈ H ₂₄ N ₄ O ₃

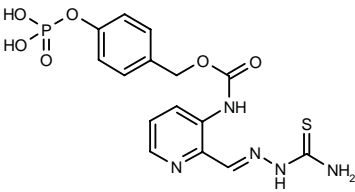
SOURCES – Harvard Med. School, Boston, MA (US); Indiana Univ., Indianapolis, IN (US).

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1. Rosowsky, A. et al. *Synthesis and antifolate activity of new tetrahydroquinazoline and dihydrocyclopenta[d]pyrimidine analogs of piritrexim and trimetrexate as potential antitumor and antiparasitic drugs*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 120.

265007+

N-[2-(Thiosemicarbazonomethyl)pyridin-3-yl]carbamic acid 4-(phosphonoxy)benzyl ester



C15-H16-N5-O6-P-S; Mol wt: 425.36

ACTION – Antineoplastic agent, a prodrug of the known ribonucleoside-diphosphate reductase inhibitor 3-AP⁺ with increased water solubility, bioavailability and resistance to *in vivo* metabolic inactivation; it was shown to be slightly more effective than the parent compound in reducing tumor growth in mice bearing M109 lung carcinoma.

SOURCE – Vion.

REFERENCES

1. Li, J. et al. (Vion Pharm., Inc.) *Prodrug forms of ribonucleotide reductase inhibitors 3-AP and 3-AMP*. US 5767134.

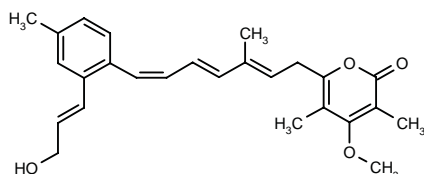
*Drug Data Rep 1998, 20(6): 535.

ANTIBIOTICS AND ALKALOIDS

BE-51068

264354

6-[7-[2-[3-Hydroxy-1(*E*)-propenyl]-4-methylphenyl]-3-methyl-2(*E*),4(*E*),6(*Z*)-heptatrienyl]-4-methoxy-3,5-dimethyl-2*H*-pyran-2-one



C26-H30-O4; Mol wt: 406.52

ACTION – Antineoplastic agent produced by culturing the microorganism *Streptomyces* sp. A51068 (FERM P-15623), with *in vitro* cytotoxicity against murine P388 leukemia (IC_{50} = 4.0 μ g/ml), murine colon cancer 26 (IC_{50} = 5.6 μ g/ml), human colon cancer DLD-1 (IC_{50} = 11 μ g/ml), human lung cancer PC-13 (IC_{50} = 5.2 μ g/ml) and human gastric cancer MKN-45 cells (IC_{50} = 12 μ g/ml).

SOURCE – Banyu.

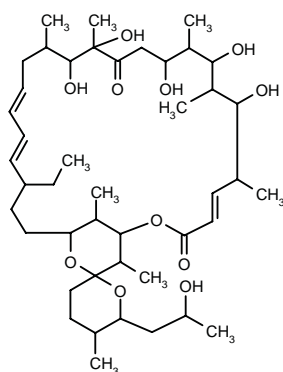
REFERENCES

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BE-56384

264357

22-Ethyl-7,9,11,14,15-pentahydroxy-6'-(2-hydroxypropyl)-5',6,8,10,14,16,28,29-octamethylspiro[2,26-dioxabicyclo[23.3.1]nonacosa-4(*E*),18(*E*),20(*E*)-triene-27,2'-tetrahydropyran]-3,13-dione



C44-H74-O11; Mol wt: 779.06

ACTION – Antineoplastic agent isolated from *Streptomyces* sp. A56384 (FERM P-15727), which exhibited *in vitro* cytotoxicity against murine P388 leukemia, murine colon cancer 26, human colon cancer DLD-1, human lung cancer PC-13 and human gastric cancer MKN-45 cells (IC_{50} = 0.10, 0.29, 34, 0.12 and 0.12 ng/ml, respectively).

SOURCE – Banyu.

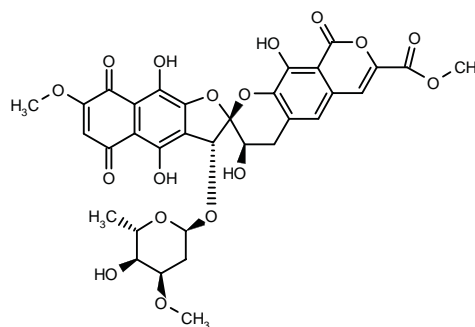
REFERENCES

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HELIQUINOMYCIN

264500

(2*S*,3*R*,3'*R*)-3'-(2,6-Dideoxy-3-*O*-methyl- α -L-altropyranosyloxy)-3,4',9',10-tetrahydroxy-7'-methoxy-5',8',9-trioxo-4,9-dihydrospiro[benzo[1,2-*b*:5,4-*c'*]dipyran-2(3*H*),2'(3'*H*)-naphtho[2,3-*b*]furan]-7-carboxylic acid methyl ester



C33-H30-O17; Mol wt: 698.59

Red powder.

ACTION – Antibiotic produced by *Streptomyces* sp. MF929-SF2 (FERM P-14380), a selective, noncompetitive inhibitor of DNA helicase with antimicrobial and antineoplastic properties. It inhibited partially purified human DNA helicase from HeLa S3 cells (K_i = 6.8 μ M) and also inhibited topoisomerase II (30 μ g/ml) and topoisomerase I (100 μ g/ml) at higher concentrations. The microbial product exhibited strong inhibitory activity against Gram-positive bacteria (MIC < 0.05-0.39 μ g/ml against *Staphylococcus aureus* strains; MIC = 0.1-0.39 μ g/ml against *Micrococcus luteus* strains; MIC = 0.1 μ g/ml against *Bacillus* spp., MIC = 0.39 μ g/ml against *Corynebacterium bovis*), but it did not show activity against Gram-negative bacteria or fungi (MIC > 50 μ g/ml). Title compound also exhibited growth-inhibitory activity against a range of cultured murine and human tumor cell lines including leukemia L1210 (IC_{50} = 0.97 μ g/ml), leukemia HL-60 (IC_{50} = 1.00 μ g/ml) and leukemia K562 (IC_{50} = 2.81 μ g/ml), carcinoma IMC (IC_{50} = 1.56 μ g/ml), melanoma B16 (IC_{50} = 0.89 μ g/ml), fibrosarcoma FS-3 (IC_{50} = 0.83 μ g/ml), uterine cancer HeLa S3 (IC_{50} = 1.62 μ g/ml), colon cancer LS180 (IC_{50} = 1.62 μ g/ml) and nasopharyngeal KB cells (IC_{50} = 1.72 μ g/ml), as well as doxorubicin- and cisplatin-resistant leukemia P388 (IC_{50} = 0.36-0.50 μ g/ml). Heliquinomycin exhibited low acute toxicity in mice (LD_{50} = 100 mg/kg i.p.).

SOURCE – Nippon Kayaku.

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2. Chino, M. et al. *Heliquinomycin, a new inhibitor of DNA helicase, produced by Streptomyces sp. MJ929-SF2 III. Biosynthesis*. J Antibiot 1997, 50(9): 781.

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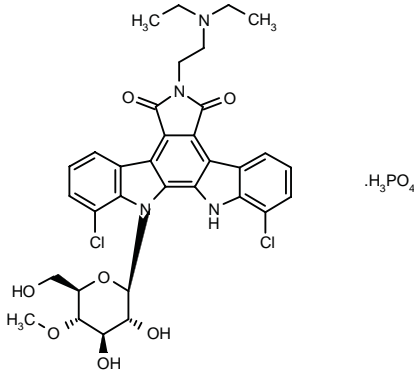
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NSC-655649

223776

1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-O-methyl-β-D-glucopyranosyl)-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione phosphate

BMS-181176
BMY-27557-01 (as HCl salt)
BMY-27557-14 (as tartrate salt)
NSC-D-640199 (as free base)



C33-H34-Cl2-N4-O7.H3-O4-P; Mol wt: 767.56

ACTION – Antineoplastic antibiotic, a water-soluble analog of rebeccamycin that intercalates into DNA and inhibits the catalytic activity of topoisomerase II. Compound demonstrated broad-spectrum *in vitro* and *in vivo* antitumor activity against solid tumors. Undergoing phase I clinical trials.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Kaneco, T. et al. (Bristol-Myers Co.) *Rebeccamycin analogs.* EP 269025, AU 8781148, JP 88198695, US 4808613.

2. Venkataram, U.V. et al. (Bristol-Myers Squibb Co.) *Stable solutions of rebeccamycin analog and preparation thereof.* EP 397147.

3. Cleary, J. et al. *Phase I clinical and pharmacokinetic study of rebeccamycin analog (NSC 655649).* Proc Amer Assoc Cancer Res 1996, 37: Abst 1132.

4. Cleary, J.F. et al. *Phase I clinical and pharmacokinetic study of a rebeccamycin analog (NSC 655649).* Proc Amer Soc Clin Oncol 1997, 16: Abst 760.

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6. Eckhardt, S.G. et al. *A phase I and pharmacokinetic (PK) study of the rebeccamycin analog NSC 655649 in patients with advanced cancer.* 7th Annu Symp Cancer Res (July 25, San Antonio) 1997, Abst 17.

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8. Kaneco, T. et al. *Water soluble derivatives of rebeccamycin.* J Antibiot 1990, 43(1): 125..

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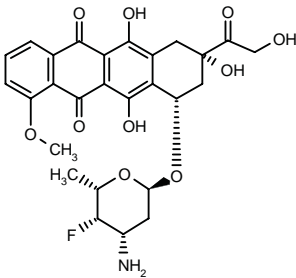
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11. Tutsch, K.D. et al. *Phase I clinical and pharmacokinetic (PK) trial of a rebeccamycin analog (NSC 655649) given as a short IV infusion daily x 3.* Proc Amer Assoc Cancer Res 1998, 39: Abst 2200.

WP-745

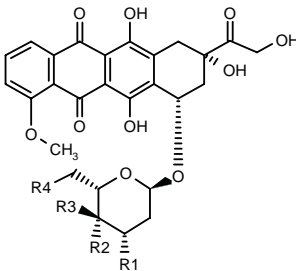
264989

4'-Fluoro-4'-deoxydoxorubicin



C27-H28-F-N-O10; Mol wt: 545.52

ACTION – Antineoplastic agent with cytotoxic activity *in vitro* against doxorubicin-sensitive and multidrug-resistant cell lines similar or superior to that of doxorubicin. Other compounds from this series of fluorinated anthracyclines are:



Compound	R1	R2	R3	R4	Formula
WP-743 [264990]	NH2	OH	H	F	C ₂₇ H ₂₈ FNO ₁₁
WP-600 [264991]	OH	F	F	H	C ₂₇ H ₂₆ F ₂ O ₁₁

SOURCE – M.D. Anderson Cancer Cent., Houston, TX (US).

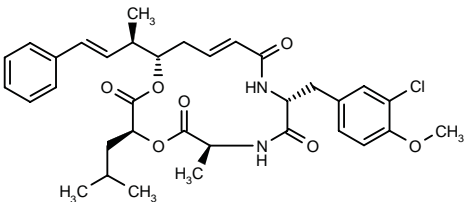
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ANTIMITOTIC DRUGS

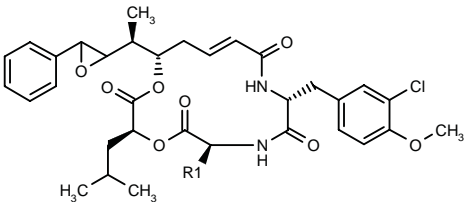
263351

[3*S*-(3α,6α,9β,12*E*,15β)]-9-(3-Chloro-4-methoxybenzyl)-3-isobutyl-6-methyl-15-[1(*R*)-methyl-3-phenyl-2(*E*)-propenyl]-1,4-dioxo-7,10-diazacyclopentadec-12-ene-2,5,8,11-tetraone

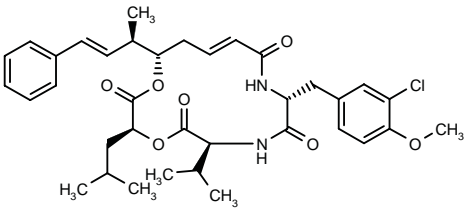


C34-H41-Cl-N2-O7; Mol wt: 625.16

ACTION – Antineoplastic and antimitotic agent, a representative compound from a novel series of cryptophycin derivatives that act by disrupting the microtubulin system. Compound is also reported to possess antifungal activity. Other related compounds include the following:



Compound	R1	Isomer	Formula
264551	Me	2 <i>S</i> ,3 <i>S</i>	C ₃₄ H ₄₁ ClN ₂ O ₈
264552	i-Pr	2 <i>R</i> ,3 <i>R</i>	C ₃₆ H ₄₅ ClN ₂ O ₈
265044	Me	2 <i>S</i> ,3 <i>S</i>	C ₃₄ H ₄₁ ClN ₂ O ₈
265045	i-Pr	2 <i>R</i> ,3 <i>R</i>	C ₃₆ H ₄₅ ClN ₂ O ₈



264550: C36-H45-Cl-N2-O7

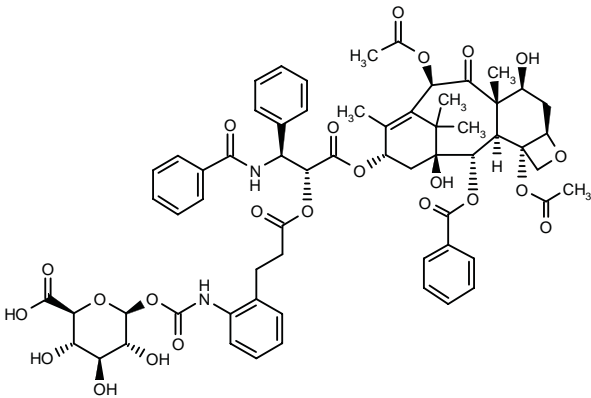
SOURCES – Univ. Hawaii, Honolulu, HI (US); Lilly; Wayne State Univ., Detroit, MI (US).

REFERENCES

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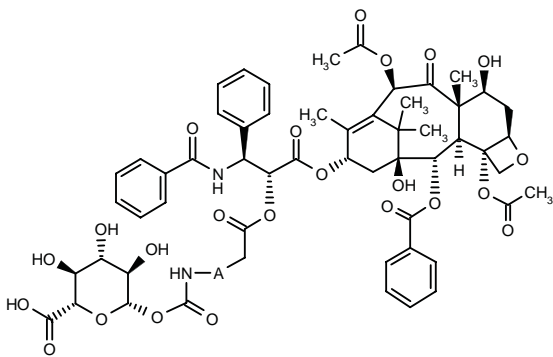
264476

[2*aR*-[2αα,4β,4αβ,6β,9α(2*R*,3*S*),11β,12α,12αα,12bα]]-6,12*b*-Diacetoxy-9-[3-benzamido-2-[3-[2-[(β-*D*-glucopyranos-1-*O*-yluronic acid)carboxamido]phenyl]propionyl-oxy]-3-phenylpropionyloxy]-12-benzoyloxy-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C63-H68-N2-O23; Mol wt: 1221.23

ACTION – Antineoplastic agent, a water-soluble paclitaxel prodrug that is activated by enzymatic cleavage. The IC₅₀ value of the prodrug against human ovarian carcinoma OVCAR-3 cells was 27 ± 3 nM and after activation by β-glucuronidase it was 1.1 ± 0.6 nM (paclitaxel = 0.22 ± 0.20 nM). Other representative compounds within this series of paclitaxel prodrugs include the following:



Compound	A	Formula
264930	-CH2C(Me)2-	C ₆₀ H ₇₀ N ₂ O ₂₃
264931	1,2-Ph	C ₆₂ H ₆₆ N ₂ O ₂₃

SOURCE – Pharmachemie.

REFERENCES

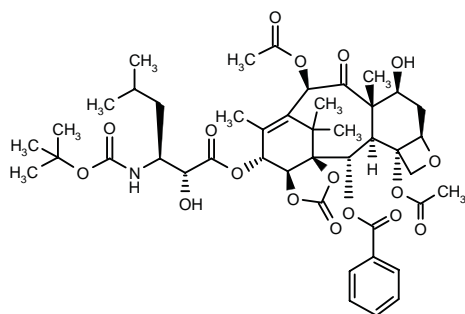
1. de Bont, H.B.A. et al. (Pharmachemie BV) *Paclitaxel prodrugs, method for preparation as well as their use in selective chemotherapy.* US 5760072.

IDN-5109

264502

[2a*R*]-[2a α ,4 β ,4a β ,6 β ,9 α (2*R*,3*S*),10 β ,11 β ,12 α ,12a α ,12b α]-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-5-methylhexanoic acid 6,12b-diacetoxy-12-benzoyloxy-10,11-carbonyldioxy-4-hydroxy-49,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester

SB-T-101131



C44-H57-N-O17; Mol wt: 871.93

ACTION – Antineoplastic agent, a taxane derivative with improved solubility. *In vitro*, it displays cytotoxicity at least equal to that of paclitaxel and docetaxel against human ovarian carcinoma A121, non-small cell lung carcinoma A549, colon carcinoma HT-29 and mammary carcinoma MCF-7 and MDA-MB231 cell lines, with IC₅₀ values of 1.2, 0.7, 1.5, 1.1 and 1.5 nM, respectively, and greater potency against human cancer cell lines expressing the multidrug resistance (MDR) phenotype (doxorubicin-resistant MCF-7 and vinblastine-resistant human leukemia CEM cells). In mice bearing various human tumor xenografts, compound was comparable in activity to the parent compound against sensitive tumors and markedly more effective against tumors resistant to paclitaxel. It was also better tolerated than paclitaxel, with a maximum tolerated dose in mice twice that of the latter (90 vs. 54 mg/kg i.v.).

SOURCES – Indena; State Univ. New York at Stony Brook, Stony Brook, NY (US).

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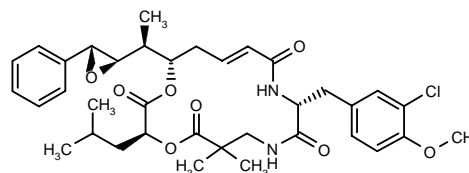
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- Distefano, M. et al. *Anti-proliferative activity of a new class of taxanes (14beta-hydroxy-10-deacetylbaccatin III derivatives) on multidrug-resistance-positive human cancer cells*. *Int J Cancer* 1997, 72(5): 844.
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LY-355703

261501

[3*S*-(3 α ,10 β ,13*E*,16 β)]-10-(3-Chloro-4-methoxybenzyl)-16-[2(*R**),3(*R**)-epoxy-1(*R*)-methyl-3-phenylpropyl]-3-isobutyl-6,6-dimethyl-1,4-dioxo-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetraone

Cryptophycin 52



C36-H45-Cl-N2-O8; Mol wt: 669.21

ACTION – Antineoplastic agent, a synthetic cryptophycin analog with broad-spectrum activity, exerting potent antiproliferative and cytotoxic activity in cultured cells (including multidrug-resistant [MDR] cells) and both human xenograft and murine tumor models, and showing no crossresistance with paclitaxel or doxorubicin. Compound inhibits microtubule polymerization *in vitro* (IC₅₀ = 0.5-0.75 μ M); it blocks cell cycle progression at G2/M and induces apoptosis.

SOURCES – Univ. Hawaii, Honolulu, HI (US); Lilly; Wayne State Univ., Detroit, MI (US).

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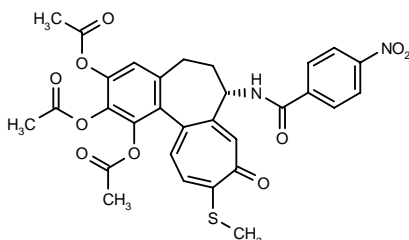
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DNA-INTERCALATING DRUGS

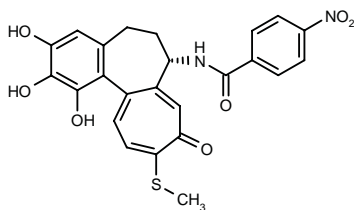
265284

4-Nitro-*N*-[1,2,3-tris(acetyloxy)-5,6,7,9-tetrahydro-10-(methylsulfonyl)-9-oxobenzo[*a*]heptalen-7(*S*)-yl]-benzamide



C30-H26-N2-O10-S; Mol wt: 606.60

ACTION – Antineoplastic agent, a thiocolchicine analog that acts as a prodrug of **265285**, an inhibitor of topoisomerase I and II (< 100 and 100% inhibition, respectively, at 100 μ M) without antitubulin activity. The prodrug was active *in vitro* against a panel of human tumor cell lines, showing significant inhibitory effect against epidermoid nasopharyngeal carcinoma KB (EC_{50} = 2.7 μ g/ml), lung carcinoma A549 (EC_{50} > 0.15 μ g/ml), breast adenocarcinoma MCF-7 (EC_{50} > 0.15 μ g/ml), renal carcinoma CAKI-1 (EC_{50} > 0.3 μ g/ml) and malignant melanoma SK-MEL-2 (EC_{50} > 0.3 μ g/ml), being more active than the parent compound.



265285: C24-H20-N2-O7-S

SOURCES – Natl. Cancer Inst., Frederick, MD (US); Univ. North Carolina, Chapel Hill, NC (US).

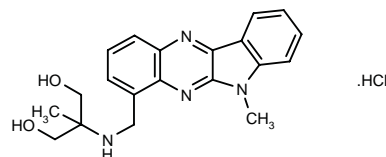
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NCA-0424*

216762

2-Methyl-2-(6-methylindolo[2,3-*b*]quinoxalin-4-yl)methylamino)propane-1,3-diol hydrochloride



C20-H22-N4-O2.HCl; Mol wt: 386.88

ACTION – Antineoplastic agent that displays potent activity *in vitro* and *in vivo* against leukemia, fibrosarcoma and melanoma. Compound exhibits inhibitory activity against topoisomerase II and intercalates into the DNA base pair.

SOURCE – Taisho.

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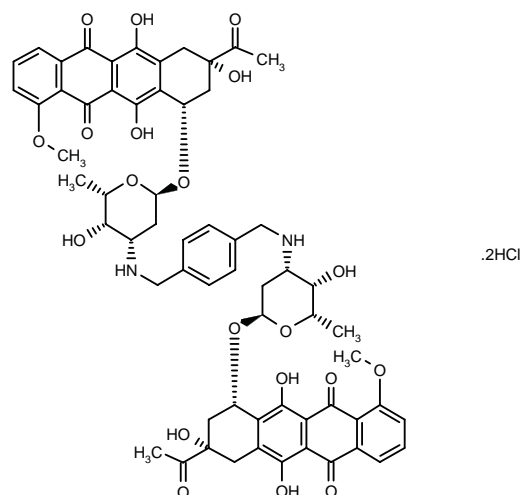
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*Identified compound **216762** Drug Data Rep 1995, 17(8): 771.

WP-631

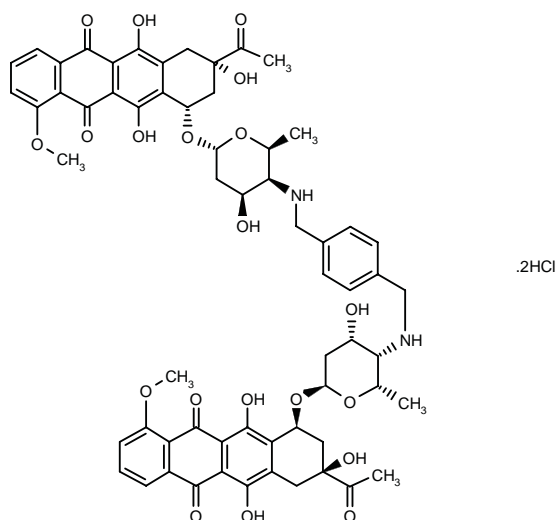
261829

N,N'-(1,4-Phenylene)bis(methylene)bis(daunomycin) dihydrochloride



C62-H64-N2-O20.2HCl; Mol wt: 1230.11

ACTION – Antineoplastic agent, a bisintercalating anthracycline that exhibits high *in vitro* activity against multidrug-resistant (MDR) cells whose resistance is mediated by multidrug resistance-associated protein (MRP). Another bisanthracycline is:



WP-652 [263482]: C62-H64-N2-O20.2HCl

SOURCES – M.D. Anderson Cancer Cent., Houston, TX (US); Univ. Mississippi, Jackson, MS (US).

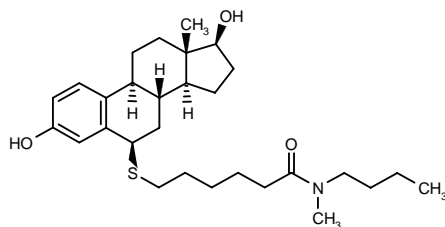
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HORMONAL AGENTS

264157

N-Butyl-6-[(6 β ,17 β)-3,17-dihydroxyestra-1,3,5(10)-trien-6-ylsulfanyl]-*N*-methylhexanamide



C29-H45-N-O3-S; Mol wt: 487.74

White foam.

ACTION – Potent and reversible inhibitor of human placental estradiol 17 β -dehydrogenase (also known as 17 β -hydroxysteroid dehydrogenase) type 1 (IC₅₀ = 0.17 μ M) with potential application in the treatment of estrogen-dependent breast cancer in conjunction with antiestrogen therapy.

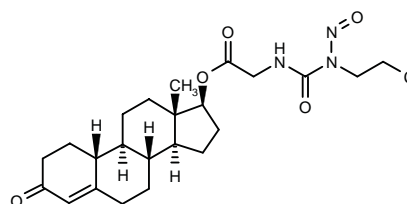
SOURCE – Laval Univ., Quebec (CA).

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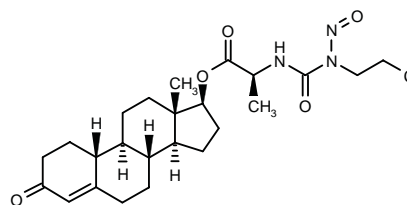
265022

N-[*N*-(2-Chloroethyl)-*N*-nitrosocarbamoyl]glycine 3-oxo-estr-4-en-17 β -yl ester



C23-H32-Cl-N3-O5; Mol wt: 465.98

ACTION – Agent for the treatment of prostate cancer, a 19-nortestosterone conjugate with affinity for androgen and progesterone receptors but none for estrogen receptors. Another compound from this series of steroid conjugates is:



265023: C24-H34-Cl-N3-O5

SOURCE – Schering AG.

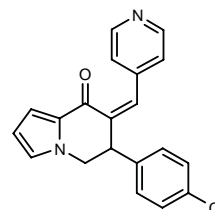
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MR-20492

263731

(*Z*)-6-(4-Chlorophenyl)-7-(pyridin-4-ylmethylene)-5,6,7,8-tetrahydroindolizin-8-one



C20-H15-Cl-N2-O; Mol wt: 334.80

Yellow crystals, m.p. 238 °C.

ACTION – Nonsteroidal aromatase inhibitor with an IC₅₀ of 0.2 μ M and a K_i of 10.3 \pm 3.3 nM for inhibition of enzyme from human placental microsomes. Compound is being evaluated *in vivo* as a potential treatment for estrogen-dependent disorders.

SOURCES – Univ. Caen, Caen (FR); CNRS.

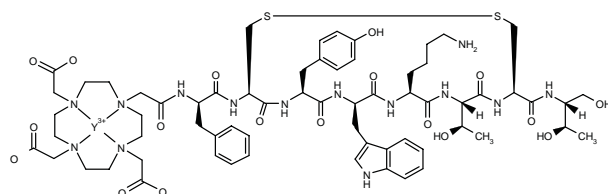
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SMT-487

264513

[N-[2-[4,7-Bis[(carboxy-κO)methyl]-10-(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-κN¹,κN⁴,κN¹⁰]acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninol cyclic (2→7)-disulfido(3→)]yttrium



C65-H89-N14-O18-S2-Y; Mol wt: 1507.54

ACTION – Somatostatin analog for the systemic delivery of radiotherapeutic nuclides to somatostatin receptor-positive tumors that binds with high affinity to human and rat somatostatin sst2 receptors (IC₅₀ = 0.9 and 0.5 nM, respectively). A single i.v. administration of 10 mCi/kg of [⁹⁰Y]-SMT-487 resulted in complete remission of tumors in 5 of 7 rat pancreatic tumor CA 20948-bearing rats, with no regrowth at 8 months after injection.

SOURCE – Novartis.

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1. Albert, R. et al. *Direct synthesis of [DOTA-DPhe]-octreotide and [DOTA-DPhe¹,Tyr⁹]-octreotide (SMT487): Two conjugates for systemic delivery of radiotherapeutic nuclides to somatostatin receptor positive tumors in man*. Bioorg Med Chem Lett 1998, 8(10): 1207.
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CANCER IMMUNOTHERAPY

TRASTUZUMAB

Prop INN

198466

Immunoglobulin G₁ (human-mouse monoclonal rhuMab HER2 γ₁-chain anti-human p185^{erbB2} receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer

Anti-HER2 MAb
HerceptinTM

ACTION – Humanized monoclonal antibody to the growth factor receptor HER2 for the treatment of HER2-overexpressing metastatic breast cancer, currently under review at the FDA. Results from phase III trials in such patients demonstrated good efficacy and tolerability as both monotherapy and in combination with chemotherapy.

SOURCES – Genentech; Mitsubishi Chem.; Roche.

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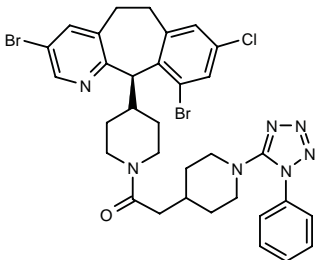
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INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

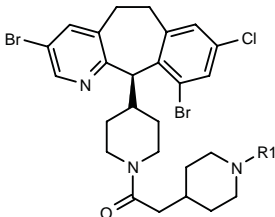
263849

3,10-Dibromo-8-chloro-11(*R*)-[1-[2-[1-(1-phenyltetrazol-5-yl)piperidin-4-yl]acetyl]piperidin-4-yl]-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine

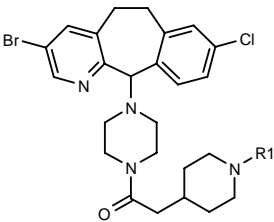


C33-H34-Br2-Cl-N7-O; Mol wt: 739.94

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras. Other specifically claimed tricyclic compounds include the following:



Compound	R1	Formula
265300	2-thiazolyl	C ₂₉ H ₃₁ Br ₂ ClN ₄ OS
265301	2-benzoxazolyl	C ₃₃ H ₃₅ Br ₂ ClN ₄ O ₂
265302	2-Pyr	C ₃₁ H ₃₃ Br ₂ ClN ₄ O
265303	2-pyrimidinyl	C ₃₀ H ₃₂ Br ₂ ClN ₅ O
265304	4-Pyr	C ₃₁ H ₃₃ Br ₂ ClN ₄ O
265308	4,5-dihydro-2-imidazolyl	C ₂₉ H ₃₄ Br ₂ ClN ₆ O
265309	4,5-dihydro-3 <i>H</i> -pyrrol-2-yl	C ₃₀ H ₃₅ Br ₂ ClN ₄ O
265310	2,3,4,6-O-(Ac)4-β-D-glucopyranosyl	C ₄₀ H ₄₈ Br ₂ ClN ₅ O ₁₀
265311	cyclopropyl	C ₂₉ H ₃₄ Br ₂ ClN ₃ O



Compound	R1	Formula
265305	5-NH2-1,2,4-triazol-3-yl	C ₂₇ H ₃₂ BrClN ₆ O
265306	5-NH2-1,2,4-oxadiazol-3-yl	C ₂₇ H ₃₁ BrClN ₇ O ₂
265307	3-NH2-1,2,4-oxadiazol-5-yl	C ₂₇ H ₃₁ BrClN ₇ O ₂

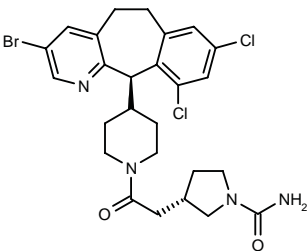
SOURCE – Schering Corp.

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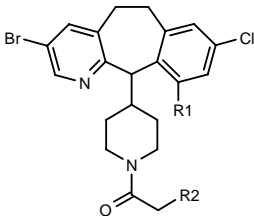
263852

2-[3(*S*)-[2-[4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl]piperidin-1-yl]-2-oxoethyl]pyrrolidin-1-yl]acetamide



C27-H31-Br2-Cl-N4-O2; Mol wt: 638.83

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC₅₀ = 0.0029 nM) and of the farnesylation of the oncogene protein Ras. Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	Isomer	Formula
265295	Cl	1-(NH2CO)- -3(<i>S</i>)-pyrrolidinyl		C ₂₆ H ₂₉ BrCl ₂ N ₄ O ₂
265296	Br	1-(NH2CO)- -3(<i>S</i>)-pyrrolidinyl	R	C ₂₆ H ₂₉ Br ₂ ClN ₄ O ₂
265297	Br	1-(NH2COCH2)- -3(<i>R</i>)-pyrrolidinyl		C ₂₇ H ₃₁ Br ₂ ClN ₄ O ₂
265298	Br	1-(MeSO2)- -3(<i>S</i>)-pyrrolidinyl	R	C ₂₆ H ₃₀ Br ₂ ClN ₃ O ₃ S
265299	Cl	1-(NH2CO)- -2(<i>S</i>)-pyrrolidinyl		C ₂₆ H ₂₉ BrCl ₂ N ₄ O ₂

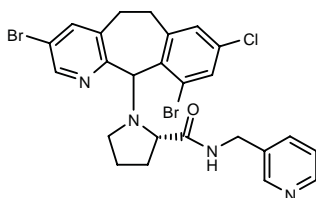
SOURCE – Schering Corp.

REFERENCES

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263853

1-(2-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridylmethyl)-pyrrolidine-2(S)-carboxamide



C25-H23-Br2-Cl-N4-O; Mol wt: 590.74

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase ($IC_{50} = 0.0052 \mu M$) and the farnesylation of the oncogene protein Ras.

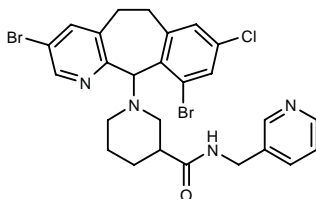
SOURCE – Schering Corp.

REFERENCES

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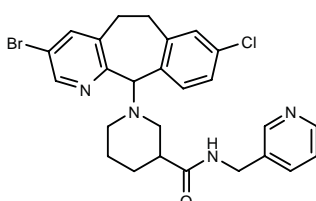
263854

1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridylmethyl)-piperidine-3-carboxamide isomer A

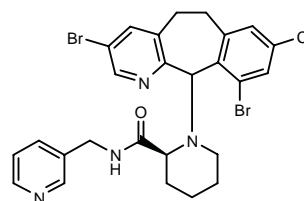


C26-H25-Br2-Cl-N4-O; Mol wt: 604.77

ACTION – Antineoplastic agent, an inhibitor of the enzyme protein farnesyltransferase. Other specifically claimed tricyclic piperidinyl compounds include the following:



Compound	Isomer	Formula
265627	B	C ₂₆ H ₂₆ Br ₂ ClN ₄ O
265628	C	C ₂₆ H ₂₆ Br ₂ ClN ₄ O
265629	D	C ₂₆ H ₂₆ Br ₂ ClN ₄ O



264898: C26-H25-Br2-Cl-N4-O: isomer D3

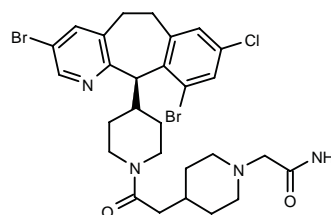
SOURCE – Schering Corp.

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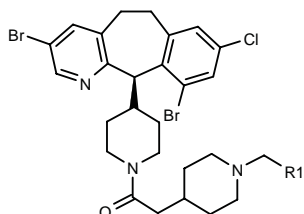
263855

(R)-2-[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidin-1-yl]-1-oxoethyl]piperidin-1-yl]acetamide



C28-H33-Br2-Cl-N4-O2; Mol wt: 652.86

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Within this series of benzocycloheptapyridines, the following are also specifically claimed:



Compound	R1	Formula
265365	CON(Me)OMe	C ₃₀ H ₃₇ Br ₂ ClN ₄ O ₃
265366	CON(Et)2	C ₃₂ H ₄₁ Br ₂ ClN ₄ O ₂
265367	CONHCH2Ph	C ₃₅ H ₃₉ Br ₂ ClN ₄ O ₂
265368	β-D-galactopyranosyl-NHCO	C ₃₄ H ₄₃ Br ₂ ClN ₄ O ₇
265369	4-morpholinyl-CO	C ₃₂ H ₃₉ Br ₂ ClN ₄ O ₃
265370	4-(t-BuOCO)-1-Piz-CO	C ₃₇ H ₄₈ Br ₂ ClN ₅ O ₄
265371	1-Piz-CO	C ₃₂ H ₄₀ Br ₂ ClN ₅ O ₂
265372	1-indoliny-CO	C ₃₆ H ₃₉ Br ₂ ClN ₄ O ₂
265373	t-BuOCO	C ₃₂ H ₄₀ Br ₂ ClN ₃ O ₃
265374	CO2H	C ₂₈ H ₃₂ Br ₂ ClN ₃ O ₃
265375	CH(OH)CH2OH	C ₂₉ H ₃₆ Br ₂ ClN ₃ O ₃

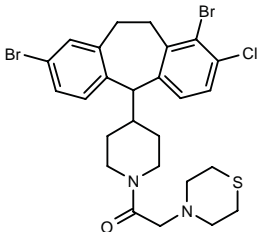
SOURCE – Schering Corp.

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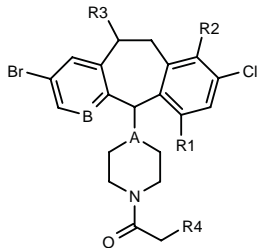
263859

4-(1,8-Dibromo-2-chloro-10,11-dihydro-5*H*-dibenzo[*a,d*]-cyclohepten-5-yl)-1-[2-(4-thiomorpholinyl)acetyl]-piperidine

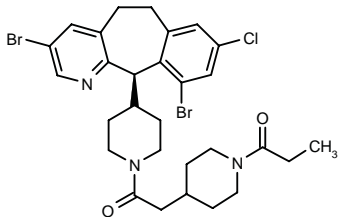


C26-H29-Br2-Cl-N2-O-S; Mol wt: 612.85

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC_{50} = 0.0089 μ M) and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds from this series of tricyclic derivatives include the following:



Compound	R1	R2	R3	R4	A	B	Formula
265312	H	Br	H	1-oxido-4-thio-morpholinyl	CH	CH	C ₂₆ H ₂₉ Br ₂ ClN ₂ O ₂ S
265313	Cl	H	Et	1-oxido-4-Pyr	N	N	C ₂₇ H ₂₇ BrCl ₂ N ₄ O ₂
265314	Cl	H	H	1,3-dioxo-2-isindolinyl	N	N	C ₂₈ H ₂₃ BrCl ₂ N ₄ O ₃



265315: C29-H34-Br2-Cl-N3-O2

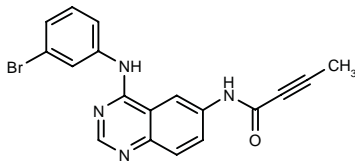
SOURCE – Schering Corp.

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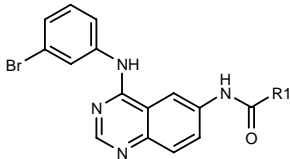
264472

N-[4-(3-Bromophenylamino)quinazolin-6-yl]-2-butyynamide



C18-H13-Br-N4-O; Mol wt: 381.23

ACTION – Antineoplastic agent, an irreversible inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase (IC_{50} = 0.002 μ M using enzyme obtained from A431 cells). *In vitro*, compound was shown to inhibit the growth of human epidermoid carcinoma A431, human breast cancer SKBR3 and Neu-3T3 cells and EGF-dependent normal human epidermal keratinocytes with IC_{50} values of 0.011, 1.057, 0.002 and 0.002 μ M, respectively. *In vivo*, compound inhibited the growth of A431 tumors implanted s.c. in mice, giving a T/C x 100 value of 17% at day 28 after tumor implantation when administered at 20 mg/kg/day i.p. x 10 days. Within this series of 4-aminoquinazolines, the following are also specifically claimed:



Compound	R1	Formula
264934	C(Me)=CH2	C ₁₈ H ₁₅ BrN ₄ O
264935	CH=CHCH=CHMe	C ₂₀ H ₁₇ BrN ₄ O
264936	(E)-CH=CHMe	C ₁₈ H ₁₅ BrN ₄ O
264937	CH=C(Me)2	C ₁₉ H ₁₇ BrN ₄ O
264938	(Z)-CH=CHCHO	C ₁₈ H ₁₃ BrN ₄ O ₂
264939	(E)-CH=CHCHO	C ₁₈ H ₁₃ BrN ₄ O ₂
264940	(E)-CH=CHCO2Et	C ₂₀ H ₁₇ BrN ₄ O ₃
264941	2-cyclopentenyl	C ₂₀ H ₁₇ BrN ₄ O
264942	vinyl	C ₁₇ H ₁₃ BrN ₄ O
264943	Ph-ethynylene	C ₂₃ H ₁₅ BrN ₄ O

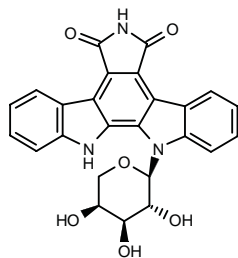
SOURCE – American Cyanamid.

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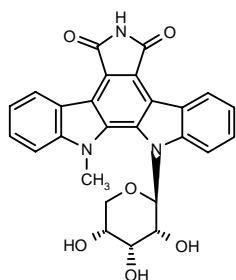
265021

12-(α -L-Arabinopyranosyl)-12,13-dihydro-5*H*-indolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione



C25-H19-N3-O6; Mol wt: 457.44

ACTION – Antineoplastic agent shown to inhibit malignant cell growth using the human non-small cell lung tumor cell line LXFL529L (IC_{50} = 0.09 μ M) and to significantly inhibit intracellular protein kinase C (PKC) activity. Another related compound is:



265241: C26-H21-N3-O6

SOURCE – Blokhin Cancer Res. Cent., Russian Acad. Med. Sci., Moscow (RU).

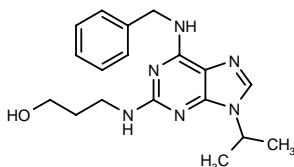
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BOHEMINE

264992

3-[6-(Benzylamino)-9-isopropyl-9*H*-purin-2-ylamino]-
propan-1-ol



C18-H24-N6-O; Mol wt: 340.43

ACTION – Antineoplastic agent that inhibits the cdc2 family of cyclin-dependent kinases and is reported to induce apoptosis in a number of tumor and leukemia cell lines *in vitro* at concentrations of 1-30 μ M, with no effect on normal cells at up to 250 μ M. In mouse models of P388D1 leukemia and B16 melanoma, compound prolonged the mean survival time or cured the animals.

SOURCE – Palacky Univ., Olomuc (CZ).

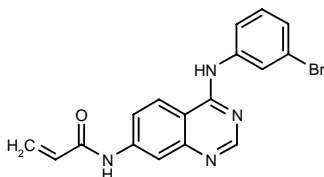
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PD-160678

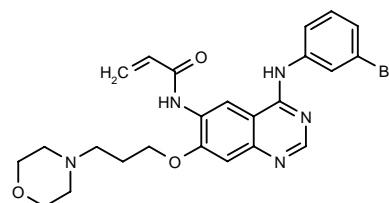
264996

N-[4-(3-Bromophenylamino)-7-quinazolinyl]-2-propenamide



C17-H13-Br-N4-O; Mol wt: 369.22

ACTION – Antineoplastic agent, a potent, selective and irreversible inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase-mediated signal transduction with an IC_{50} of 0.36 nM for kinase activity and of 14 nM in the autophosphorylation assay in human epidermoid carcinoma A-431 cells. It inhibited the proliferation of human epidermoid carcinoma A-431 cells with an IC_{50} of $0.30 \pm 0.09 \mu M$. Antitumor activity was also demonstrated *in vivo* against a range of human tumor xenografts; for example, in nude mice implanted with NIH 3T3 fibroblasts transfected with the human EGF receptor, at 100 and 30 mg/kg i.p. b.i.d. on days 3-7 it inhibited tumor growth by 40-50%. Another quinazoline is:



PD-169540 [264997]: C24-H26-Br-N5-O3

SOURCE – Warner-Lambert.

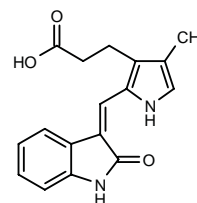
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SU-5402

265028

(Z)-3-[4-Methyl-2-(2-oxo-3,4-dihydroindol-3-ylmethylene)-pyrrol-3-yl]propionic acid



C17-H16-N2-O3: Mol wt: 296.33

Yellow solid.

ACTION – Protein tyrosine kinase inhibitor proven effective in inhibiting the kinase activity of fibroblast growth factor (FGF) receptor 1 (FGFR1) *in vitro* with an IC_{50} of 10-20 μM ; it also inhibited acidic FGF-induced FGFR1 autophosphorylation in NIH 3T3 cells (IC_{50} = 10-20 μM), and other FGFR1 kinase activity-dependent events such as acidic FGF-induced tyrosine phosphorylation of a phosphoprotein (pp90) and the mitogen-activated protein kinases ERK1 and ERK2. SU-5402 inhibited [3H]-thymidine incorporation in response to acidic FGF stimulation. The compound has also been shown to be a potent inhibitor of the vascular endothelial growth factor (VEGF) receptor FLK.

SOURCE – Sugen.

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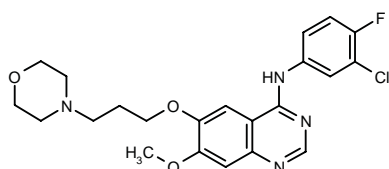
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3. Shawver, L.K. et al. *In vitro activity, anti-tumor efficacy and pharmacokinetics of indolin-2-one VEGF receptor inhibitors*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 289.

ZD-1839*

233069

244386 (as hydrochloride)

4-(3-Chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazoline



C22-H24-F-Cl-N4-O3; Mol wt: 446.91

ACTION – Antineoplastic agent, a potent and selective inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase ($IC_{50} = 0.02 \mu M$). ZD-1839 inhibited *in vitro* the EGF-stimulated growth of the human nasopharyngeal cancer KB cell line with an IC_{50} of $0.1 \mu M$. In athymic nude mice, it inhibited the growth of xenografts of the human vulval epidermoid carcinoma cell line A-431 with an ED_{50} of approximately 12.5 mg/kg p.o. Compound demonstrated favorable pharmacokinetics and safety following once-daily oral administration (10-100 mg) to healthy male volunteers.

SOURCE – Zeneca.

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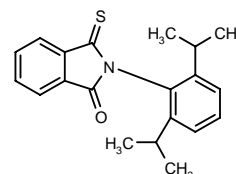
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2. Kelly, H.C. et al. *Phase I data of ZD1839 - an oral epidermal growth factor receptor tyrosine kinase inhibitor*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 419.
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6. *Zeneca's strong R&D performance set to continue*. Zeneca Group plc Press Release 1995, December 12.
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*Identified compound **244386** Drug Data Rep 1997, 19(3): 271.

ANTIANGIOGENIC AGENTS

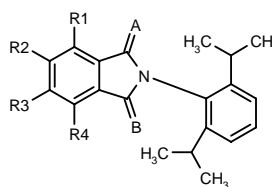
262830

2-(2,6-Diisopropylphenyl)-3-thioxoisindolin-1-one



C20-H21-N-O-S; Mol wt: 323.45

ACTION – An inhibitor of neovascularization that shows tumor necrosis factor (TNF- α) production-regulating activity. Within this series of phthalimido derivatives, the following are also included:



Compound	R1=R3=R4	R2	A	B	Formula
264058	H	H	O	H2	C ₂₀ H ₂₃ NO
264059	H	Me	O	O	C ₂₁ H ₂₃ NO ₂
264060	F	F	S	O	C ₂₀ H ₁₇ F ₄ NOS

Certain compounds within the scope of the invention also inhibit aminopeptidase N (microsomal aminopeptidase).

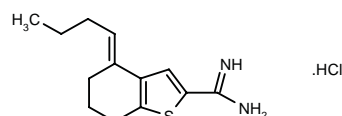
SOURCE – Ishihara Sangyo.

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263847

4-Butylidene-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide hydrochloride



C13-H18-N2-S.HCl; Mol wt: 270.82

ACTION – An inhibitor of urokinase (also known as urokinase-type plasminogen activator or uPA; $IC_{50} = 0.47 \mu M$) with potential in the treatment of angiogenesis, metastasis, osteoporosis, rheumatoid arthritis and other inflammatory disorders, and also as a contraceptive.

SOURCE – Fujisawa.

REFERENCES

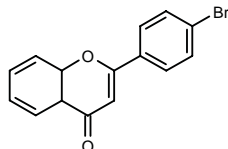
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MISCELLANEOUS ANTINEOPLASTIC AGENTS

261643

2-(4-Bromophenyl)-4*H*-1-benzopyran-4-one

4'-Bromoflavone



C₁₅H₁₁-Br-O₂; Mol wt: 303.15

ACTION – Potential chemopreventive agent that strongly induces phase II enzymes. Compound potently increased quinone reductase activity in murine hepatoma Hepa 1c1c7 cells and also significantly and dose-dependently induced enzyme activity and glutathione levels in rat liver, mammary gland, colon, stomach and lung; the induction potential in Hepa 1c1c7 cells was comparable to that of β -naphthoflavone but it was less cytotoxic (IC₅₀ > 100 μ M vs. 8 μ M). Protein expression of two major detoxification isoforms of glutathione *S*-transferase was observed in cell culture and compound inhibited DMBA-induced mutagenesis in *Salmonella typhimurium*.

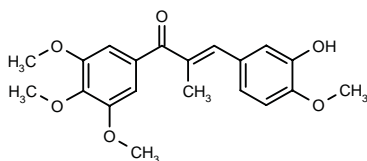
SOURCE – Univ. Illinois at Chicago, Chicago, IL (US).

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263732

3-(3-Hydroxy-4-methoxyphenyl)-2-methyl-1-(3,4,5-trimethoxyphenyl)-2(*E*)-propen-1-one



C₂₀-H₂₂-O₆; Mol wt: 358.39

ACTION – Antineoplastic agent structurally similar to combretastatin A4, proven to potently inhibit cell growth *in vitro* (IC₅₀ = 0.21 nM against human myeloid leukemia K562 cells). Cytotoxic activity has also been reported against human epithelioid carcinoma HeLaS3 cells (IC₅₀ = 0.62 nM).

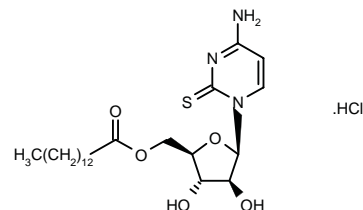
SOURCES – Univ. Manchester Inst. Sci. Technol., Manchester (GB); Paterson Inst. Cancer Res., Manchester (GB).

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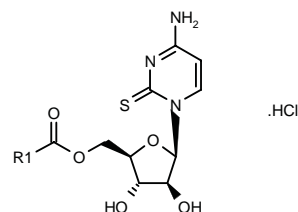
264360

1-(5-*O*-Tetradecanoyl- β -D-arabinofuranosyl)-2-thiocytosine hydrochloride



C₂₃-H₃₉-N₃-O₅-S.HCl; Mol wt: 506.10

ACTION – Antineoplastic agent shown to increase survival in mice bearing P388 leukemia (ILS = 63 and > 120% at 100 and 300 mg/kg/day i.p. x 5 days, respectively). Other compounds from this series of 2-thiocytosine derivatives include the following:



Compound	R1	Formula
265636	C17H35	C ₂₇ H ₄₇ N ₃ O ₅ S.HCl
265637	C19H39	C ₂₉ H ₅₁ N ₃ O ₅ S.HCl
265638	C21H43	C ₃₁ H ₅₅ N ₃ O ₅ S.HCl
265639	C23H47	C ₃₃ H ₅₉ N ₃ O ₅ S.HCl
265640	(Z)-(CH ₂) ₇ CH=CH(CH ₂) ₇ CH ₃	C ₂₇ H ₄₅ N ₃ O ₅ S.HCl

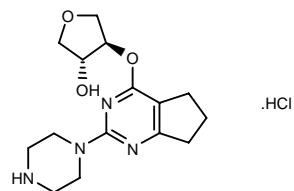
SOURCE – Toagosei.

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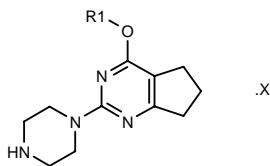
264428

4-[4(*R*)-Hydroxytetrahydrofuran-3(*R*)-yloxy]-2-(1-piperazinyl)-6,7-dihydro-5*H*-cyclopentapyrimidine hydrochloride

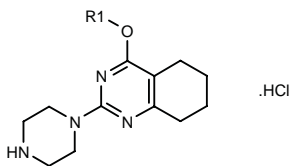


C₁₅-H₂₂-N₄-O₃.HCl; Mol wt: 342.82

ACTION – Antineoplastic agent that acts by inhibiting blood flow into tumor tissues, as demonstrated in mice bearing colon 26 tumors at a dose of 0.005 mg/kg i.v. Antitumor activity was demonstrated *in vivo* in nude mice bearing human gastric cancer St-4 xenografts (T/C x 100 = 30.1% at 30 mg/kg/day p.o. x 40 days). Other compounds from this series of pyrimidine derivatives include the following:



Compound	R1	X	Formula
265443	3t,4t-(OH)2-1r-cyclopentyl	HCl	C ₁₆ H ₂₄ N ₄ O ₃ .HCl
265444	4(S)-OH-3(S)-THF	HCl	C ₁₅ H ₂₂ N ₄ O ₃ .HCl
265445	2(R),3(R),4(S)-(OH)3-1(R)-cyclopentyl		C ₁₆ H ₂₄ N ₄ O ₄
265451	(R)-CH2CH2CH(OH)CH2OH		C ₁₅ H ₂₄ N ₄ O ₃
265453	2(R),3(S)-(OH)-4(S)-MeO-1(R)-cyclopentyl	fumarate	C ₁₇ H ₂₆ N ₄ O ₄ .C ₄ H ₄ O ₄



Compound	R1	Formula
265446	3t,4t-(OH)2-1r-cyclopentyl	C ₁₇ H ₂₆ N ₄ O ₃ .HCl
265448	2(R),3(S)-(OH)-4(S)-MeO-1(R)-cyclopentyl	C ₁₈ H ₂₈ N ₄ O ₄ .HCl
265449	4(R)-OH-3(R)-THF	C ₁₆ H ₂₄ N ₄ O ₃ .HCl
265450	4(S)-OH-3(S)-THF	C ₁₆ H ₂₄ N ₄ O ₃ .HCl
265452	(R)-CH2CH2CH(OH)CH2OH	C ₁₆ H ₂₆ N ₄ O ₃ .HCl

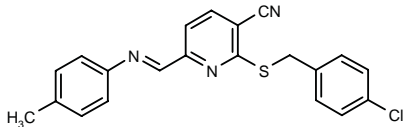
SOURCE – Kanebo.

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264474

(E)-2-(4-Chlorobenzylsulfanyl)-6-(4-methylphenylimino-methyl)pyridine-3-carbonitrile



C21-H16-Cl-N3-S; Mol wt: 377.89

ACTION – Antineoplastic agent, an inhibitor of human telomerase (IC₅₀ = 29 μM) with no effect on other related enzymes such as DNA polymerase I, HeLa RNA polymerase II, T3 RNA polymerase, MMLV reverse transcriptase and topoisomerase I. At 10 μM, it was found to induce a decrease in telomere length in human ovarian cancer OVCAR-5 and SK-OV-3 cells, while having no effect on normal fibroblast BJ cells.

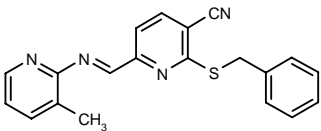
SOURCE – Geron.

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265008

2-(Benzylsulfanyl)-6-(3-methylpyridin-2-yliminomethyl)-pyridine-3-carbonitrile



C20-H16-N4-S; Mol wt: 344.43

ACTION – Antineoplastic agent, an inhibitor of telomerase (IC₅₀ < 3.2 μM).

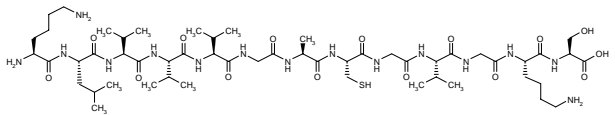
SOURCE – Geron.

REFERENCES

1. Gaeta, F.C.A. and Stracker, E.C. (Geron Corp.) *Telomerase inhibitors*. US 5767278.

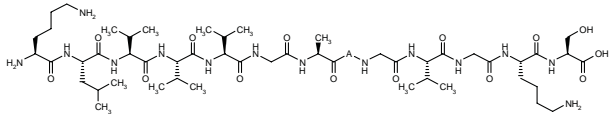
265009¹⁻³

L-Lysyl-L-leucyl-L-valyl-L-valyl-L-valyl-glycyl-L-alanyl-L-cysteinyl-glycyl-L-valyl-glycyl-L-lysyl-L-serine



C53-H97-N15-O15-S; Mol wt: 1216.50

ACTION – Mutant *ras* p21 oncogene peptide with point mutations at position 12 of *ras* p21, which are associated with a range of human carcinomas. Clinical studies (phase I trials) in patients with metastatic carcinoma whose primary tumors had mutations in the K-*ras* protooncogene at codon 12 demonstrated that compound administered in Detox adjuvant induced a highly specific and systemic anti-*ras* cellular immune response at both the CD4+ and CD8+ T-cell level, with no detectable crossreactivity against normal proto-*ras* sequences. Potentially useful as an oncogene-specific cancer vaccine for active or passive immunotherapy. Other related peptides include the following:



Compound	A	Formula
265010 ¹⁻³	-L-Asp-	C ₅₄ H ₉₇ N ₁₅ O ₁₇
265011 ¹⁻⁴	-L-Val-	C ₅₅ H ₁₀₁ N ₁₅ O ₁₅

SOURCE – Natl. Cancer Inst., Bethesda, MD (US).

REFERENCES

1. Schlom, J. and Abrams, S. (Dept. Health Human Services [USA]) *Mutated ras peptides for generation of CD8+ cytotoxic T lymphocytes*. WO 9740156.

2. Abrams, S.I. et al. *Generation of stable CD4+ and CD8+ T cell lines from patient immunized with ras oncogene-derived peptides reflecting coden mutations*. Cell Immunol 1997, 182(2): 137.

3. Gupta, S.L. et al. *Formulation development of point-mutated p21 ras-derived synthetic peptides*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 179.

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CANCER GENE THERAPY

SCH-58500

259637

Recombinant adenovirus encoding human wild-type p53 gene

rAd/p53

ACTION – A replication-defective recombinant adenovirus encoding the human *p53* tumor suppressor gene that acts as a gene delivery system in tumor cells. In a series of human cell lines, the gene therapy inhibited the growth of cells expressing no *p53* and various mutant *p53* proteins, while it had no effect on cells containing wild-type *p53*. *In vivo*, it suppressed tumor growth and increased survival in nude mice bearing tumors expressing mutant *p53*. Currently being evaluated in clinical trials in patients with various cancers.

SOURCES – Univ. California, Oakland, CA (US); Schering-Plough.

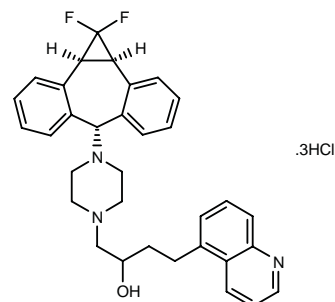
REFERENCES

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2. Lee, W.-H. and Chen, P.-L. (Univ. California) *Genetic mechanisms of tumor suppression*. EP 475623.
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4. Harris, M.P. et al. *Adenovirus-mediated p53 gene transfer inhibits growth of human tumor cells expressing mutant p53 protein*. Cancer Gene Ther 1996, 3(2): 121.
5. Koeck, H. et al. *Adenovirus-mediated p53 gene transfer suppresses growth of human glioblastoma cells in vitro and in vivo*. Int J Cancer 1996, 67(6): 808.
6. Maneval, D.C. et al. *Recombinant p53 adenovirus (rAd/p53) effects on proliferation of human tumor cell lines*. J Cell Biochem 1994, (Suppl. 18D): Abst R 508.
7. Venook, A.P. et al. *Gene therapy of colorectal liver metastases using a recombinant adenovirus encoding wt p53 (SCH 58500) via hepatic artery infusion: A phase I study*. Proc Amer Soc Clin Oncol 1998, 17: Abst 1661.
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RESISTANCE MODIFIERS

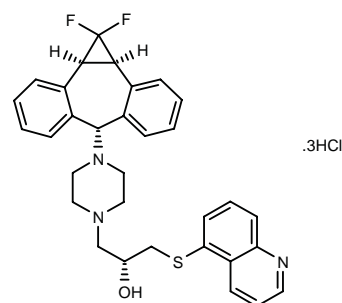
264676

anti-1-[4-[1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo-[a,e]cyclopropa[c]cyclohepten-6-yl]piperazin-1-yl]-4-(5-quinolinyl)-2-butanol trihydrochloride



C33-H33-F2-N3-O.3HCl; Mol wt: 635.02

ACTION – Drug resistance and multidrug resistance modulator that acts via an interaction with P-glycoprotein, particularly useful for the treatment of drug-resistant and multidrug-resistant cancer and drug-resistant malaria. Due to its action on P-glycoprotein, compound may also be useful for enhancing the ability of a drug to cross the blood-brain barrier, as well as for enhancing the oral bioavailability of a drug. Another related compound is:



265294: C32-H31-F2-N3-O-S.3HCl

SOURCE – Lilly.

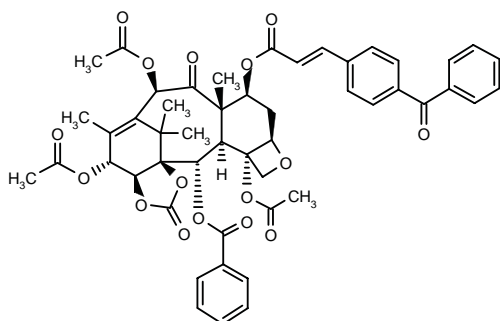
REFERENCES

1. Kroin, J.S. and Norman, B.H. (Eli Lilly & Co.) *Drug resistance and multidrug resistance modulators*. EP 844244, WO 9822112.

SB-RA-131012

264732

[2a*R*-(2α,4β,4αβ,6β,9α,10β,11β,12α,12α,12bα)]-6,9,12b-Triacetoxyl-12-benzoyloxy-4-[3-(4-benzoylphenyl)-2(*E*)-propenoyloxy]-10,11-(carbonyldioxy)-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclododeca[3,4]benz-[1,2-*b*]oxet-5-one



C50-H48-O16; Mol wt: 904.92

ACTION – Noncytotoxic hydrophobic taxane derivative with potent multidrug resistance (MDR)-reversing activity. Compound was shown to block the efflux mechanism of the P-glycoprotein pump, allowing anticancer agents to penetrate into and accumulate in MDR cancer cells, as demonstrated against the drug-resistant human breast cancer cell lines MCF-7/MDR and MDA-435/LCC6-MDR when coadministered with paclitaxel (92-94% reversal at 0.1 μM and 95-99% reversal at 1 μM).

SOURCES – State Univ. New York at Stony Brook, Stony Brook, NY (US); Roswell Park Cancer Inst., Buffalo, NY (US).

REFERENCES

1. Ojima, I. et al. *Discovery and development of new taxanes as highly efficient reversal agents for multi-drug resistance in cancer cells*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 557.
2. Ojima, I. et al. *Structure-activity relationship studies of new taxanes as reversal agents for multi-drug resistance in cancer cells*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 012.

OCULAR MEDICATIONS

OCULAR ANTIINFLAMMATORY AND ANTIINFECTIVE AGENTS

LOTEPREDNOL ETABONATE⁺

Rec INN: USAN

170014

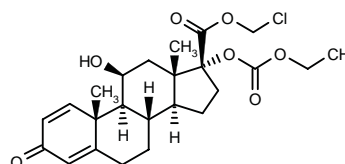
11β,17-Dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid chloromethyl ester 17-(ethylcarbonate)

17α-(Ethoxycarbonyloxy)-11β-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester

CDDD-5604

HGP-1

P-5604



C24-H31-Cl-O7; Mol wt: 466.96

ACTION – Topical, site-specific antiinflammatory corticosteroid for ophthalmic use.

INDICATION – 0.5%: Treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis and cyclitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation, and also for the treatment of postoperative inflammation following ocular surgery. 0.2%: Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

PRESENTATION – 0.5%: Bottles (ophthalmic suspension), 2.5, 5, 10 and 15 ml containing 5 mg loteprednol etabonate/ml (0.5%); 0.2%: Bottles (ophthalmic suspension), 5 and 10 ml containing 2 mg loteprednol etabonate/ml (0.2%).

PROPRIETARY NAMES – *Alex* (0.2%; US); *Lotemax* (0.5%; US).

SOURCES – Pharmos; codeveloped, manufactured and marketed by Bausch & Lomb.

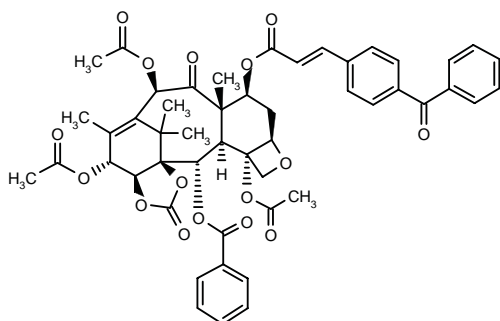
RECENT REFERENCES

1. Guy, Y.J. and Friedman, D. (Pharmos Corp.) *Suspension of loteprednol etabonate*. WO 9511669.
2. Bodor, N. *Design of soft corticosteroids*. IBC 7th Annu Conf Asthma Allergy (Oct 27-28, Pentagon City) 1997.
3. Dell, S.J. et al. *A controlled evaluation of the efficacy and safety of loteprednol etabonate in the prophylactic treatment of seasonal allergic conjunctivitis*. *Amer J Ophthalmol* 1997, 123(6): 791.
4. Friedlaender, M.H. and Howes, J. *A double-masked, placebo-controlled evaluation of the efficacy and safety of loteprednol etabonate in the treatment of giant papillary conjunctivitis*. *Amer J Ophthalmol* 1997, 123(4): 455.

SB-RA-131012

264732

[2a*R*-(2α,4β,4aβ,6β,9α,10β,11β,12α,12α,12bα)]-6,9,12b-Triacetoxyl-12-benzoyloxy-4-[3-(4-benzoylphenyl)-2(*E*)-propenoyloxy]-10,11-(carbonyldioxy)-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclododeca[3,4]benz-[1,2-*b*]oxet-5-one



C50-H48-O16; Mol wt: 904.92

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OCULAR MEDICATIONS

OCULAR ANTIINFLAMMATORY AND ANTIINFECTIVE AGENTS

LOTEPREDNOL ETABONATE⁺

Rec INN: USAN

170014

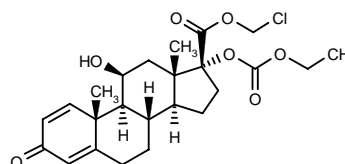
11β,17-Dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid chloromethyl ester 17-(ethylcarbonate)

17α-(Ethoxycarbonyloxy)-11β-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester

CDDD-5604

HGP-1

P-5604



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6. Howes, J. and Strahlman, E. *A randomized, double-masked, placebo controlled, parallel group study of the effects of loteprednol etabonate 0.2% ophthalmic suspension (LE) in patients with seasonal allergic conjunctivitis*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2020.

7. Howes, J. and Novack, G.D. *Failure to detect systemic levels, and effects of loteprednol etabonate and its metabolite, PJ-91, following chronic ocular administration*. J Ocul Pharmacol Ther 1998, 14(2): 153.

8. Poppe, H. et al. *Effects of loteprednol etabonate on TNF α and GM-CSF release in vitro and on late phase allergic eosinophilia in guinea pigs administered intratracheally as a dry powder*. Amer J Respir Crit Care Med 1998, 157(3): A522.

9. Rachwal, S. et al. *Synthesis and structural studies by NMR of some steroids related to loteprednol etabonate*. 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst ORGN 501.

10. Strahlman, E. and Howes, J. *A randomized, double-masked, placebo controlled, parallel group study of the effects of loteprednol etabonate 0.2% ophthalmic suspension (LE) in patients with seasonal allergic conjunctivitis*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1025.

11. Zbyszynski, B. et al. *A randomized, double-masked, placebo controlled paired comparison of loteprednol etabonate 0.5% ophthalmic suspension (LE) BID or QID versus placebo in an antigen challenge model of acute allergic conjunctivitis*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2012.

12. *Bausch & Lomb Pharmaceuticals and Pharmos Corporation receive FDA approval to market Lotemax™ and Altrex™*. Bausch & Lomb Pharmaceuticals/Pharmos Corporation 1998, May 10.

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MONOGRAPH – Graul, A. et al. *Loteprednol etabonate*. Drugs Fut 1997, 22(10): 1086.

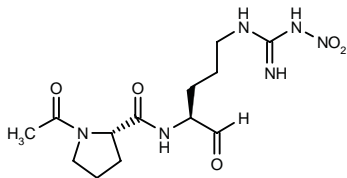
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

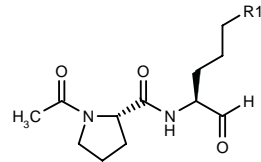
261189

Acetyl-propyl-(N^ω-nitro)argininal



C13-H22-N6-O5; Mol wt: 342.35

ACTION – Agent for the treatment of osteoporosis, an inhibitor of cathepsin K (IC₅₀ = 0.016 μM) with selectivity over other cysteine proteases such as cathepsin B, cathepsin L, papain, trypsin, chymotrypsin and thrombin (IC₅₀ = 2.7, > 10, 0.33, > 10, > 10 and > 10 μM, respectively). Within this series of proline derivatives, the following are also included:



Compound	R1	Formula
265065	NHC(=NH)NH2	C ₁₃ H ₂₃ N ₅ O ₃
265066	Me	C ₁₃ H ₂₂ N ₂ O ₃

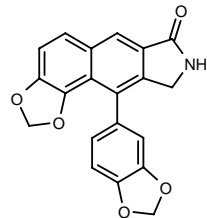
SOURCE – Yamanouchi.

REFERENCES

1. Aibe, K. et al. (Yamanouchi Pharm. Co., Ltd.) *Bone resorption inhibitors*. WO 9801133.

263297

10-(1,3-Benzodioxol-5-yl)-8,9-dihydro-7H-1,3-benzodioxolo[4,5-f]isoindol-7-one



C20-H13-N-O5; Mol wt: 347.33

ACTION – Agent for the treatment of bone and cartilage disorders such as osteoporosis and arthritis, and neuronal disorders such as Alzheimer’s disease, motor neuronal disorders and diabetic peripheral neuropathy, with bone morphogenetic protein (BMP)- and neurotrophic factor-like activity. Compound may also be used to enhance the activity of BMP and neurotrophic factors. Its BMP-like activity was demonstrated by induction of alkaline phosphatase activity in cultured murine osteoblast MC3T3-E1 cells at 0.01 μM. At this concentration, it was also found to enhance the activity of coadministered BMP, as measured by increased alkaline phosphatase activity in the presence of compound. In addition, it was found to enhance nerve growth factor (NGF) activity in pheochromocytoma PC12 cells at 0.01 μM, as measured by neurite extension using a microscope. Other compounds from this series of naphtholactams and lactones include the following:

5. George, M. et al. *A randomized, double-masked, placebo controlled paired comparison of loteprednol etabonate 0.1%, 0.2% or 0.3% ophthalmic suspension (LE) versus placebo in an antigen challenge model of acute allergic conjunctivitis*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2019.

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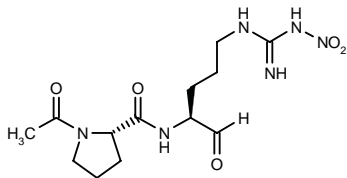
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

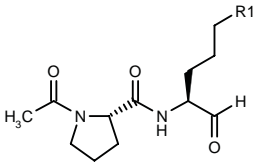
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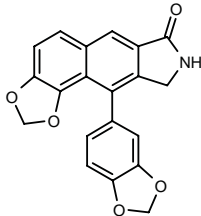
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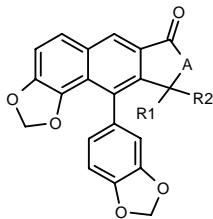
263297

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Compound	R1	R2	A	Formula
264029	H	H	N(Et)	C ₂₂ H ₁₇ NO ₅
264030	H	H	N(i-Pr)	C ₂₃ H ₁₉ NO ₅
264031	H	H	CH ₂ NH	C ₂₁ H ₁₅ NO ₅
264032	H	H	CH ₂	C ₂₁ H ₁₄ O ₅
264033		-O-	NH	C ₂₀ H ₁₁ NO ₆
264034	H	H	N(2-Pyr)	C ₂₅ H ₁₆ N ₂ O ₅

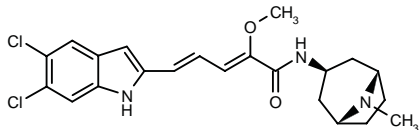
SOURCE – Takeda.

REFERENCES

1. Marui, S. et al. (Takeda Chem. Ind., Ltd.) *Naphtholactams and lactones as bone morphogenetic protein active agents*. WO 9807705.

264588

exo-5-(5,6-Dichloro-1*H*-indol-2-yl)-2-methoxy-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2(*Z*),4(*E*)-penta-dienamide



C22-H25-Cl2-N3-O2; Mol wt: 434.36

Hydrochloride, yellow powder *m.p.* > 250 °C.

ACTION – Potent and selective inhibitor of osteoclast vacuolar H⁺-ATPase (V-ATPase) proven effective *in vitro* against enzyme from chicken osteoclast membranes (IC₅₀ = 0.1 μM); it inhibited V-ATPase from chicken adrenal gland and human kidney cortex with IC₅₀ values of 2.5 and 1.32 μM, respectively, whereas the nonselective V-ATPase inhibitor bafilomycin A₁ nonspecifically inhibited the V-ATPase pump in the three different tissues with IC₅₀ values of 0.1-0.2 nM. Title compound prevented bone resorption by human osteoclasts (IC₅₀ = 0.03 μM). Potentially useful as a lead for developing drugs for the treatment of osteoporosis.

SOURCE – SmithKline Beecham.

REFERENCES

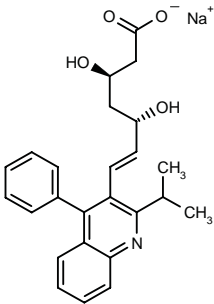
1. Farina, C. et al. (SmithKline Beecham SpA) *Indole derivs. useful in the treatment of osteoporosis*. WO 9621644.

2. Gagliardi, S. et al. 5-(5,6-Dichloro-2-indolyl)-2-methoxy-2,4-pentadienamides: *Novel and selective inhibitors of the vacuolar H⁺-ATPase of osteoclasts with bone antiresorptive activity*. J Med Chem 1998, 41(10): 1568.

TREATMENT OF LIPOPROTEIN DISORDERS

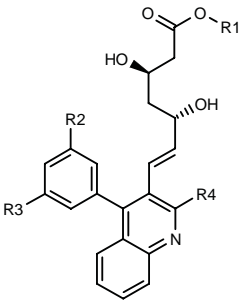
263743

3(*R*),5(*S*)-Dihydroxy-7-(2-isopropyl-4-phenylquinolin-3-yl)-6(*E*)-heptenoic acid sodium salt

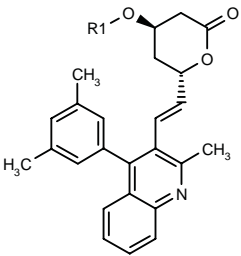


C25-H26-N-Na-O4; Mol wt: 427.47

ACTION – Hypolipidemic agent, an inhibitor of cholesterol biosynthesis that acts by inhibition of HMG-CoA reductase activity. Other specifically claimed quinoline analogs of mevalonolactone include the following:



Compound	R1	R2=R3	R4	Formula
263939	Et	H	i-Pr	C ₂₇ H ₃₁ NO ₄
263940	Na	Me	Me	C ₂₅ H ₂₆ NNaO ₄
263941	Et	Me	Me	C ₂₇ H ₃₁ NO ₄



Compound	R1	Formula
263942	Na	C ₂₅ H ₂₄ NNaO ₃
263943	H	C ₂₅ H ₂₅ NO ₃

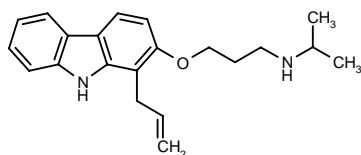
SOURCE – Novartis.

REFERENCES

1. Wattanasin, S. (Novartis Pharm. Corp.) *Quinoline analogs of mevalonolactone and derivs. thereof*. US 5753675.

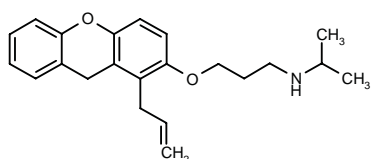
263881

N-[3-(1-Allyl-9*H*-carbazol-2-yloxy)propyl]-*N*-isopropylamine



C21-H26-N2-O; Mol wt: 322.45

ACTION – Hypolipidemic agent, a potent inhibitor of squalene synthase (IC_{50} = 32 nM in human hepatoma Hep G2 cells). It reduced blood cholesterol levels in rats fed a cholesterol-enriched diet by 50% at a dose of 50 mg/kg p.o. Another representative compound within this series of tricyclic fused ring derivatives is:



264709: C22-H27-N-O2

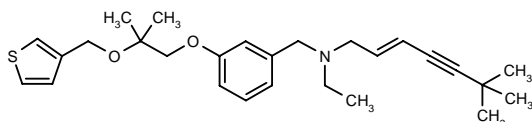
SOURCE – Yamanouchi.

REFERENCES

1. Matsuda, K. et al. (Yamanouchi Pharm. Co., Ltd.) *Novel tricyclic fused ring derivs.* WO 9812170.

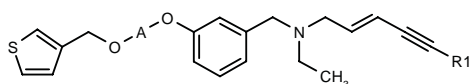
263357

(*E*)-*N*-(6,6-Dimethylhept-2-en-4-ynyl)-*N*-ethyl-*N*-[3-[2-methyl-2-(3-thienylmethoxy)propoxy]benzyl]amine



C27-H37-N-O2-S; Mol wt: 439.65

ACTION – Hypolipidemic and hypocholesterolemic agent, an inhibitor of squalene epoxidase (IC_{50} = 5.4 nM against enzyme from human Hep G2 cells) shown to potently inhibit cholesterol synthesis *in vitro* in Hep G2 cells (IC_{50} = 2.2 nM). Other specifically claimed compounds from this series of substituted amine derivatives include the following:



Compound	R1	A	Formula
264311	C(Me)2OMe	-C(Me)2CH2-	C ₂₇ H ₃₇ NO ₃ S
264312	t-Bu	-CH2C(Me)2-	C ₂₇ H ₃₇ NO ₂ S

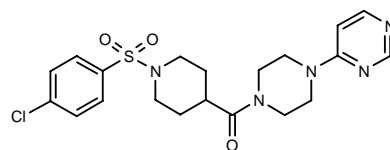
SOURCE – Fujisawa.

REFERENCES

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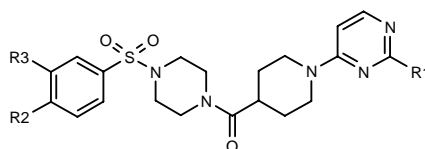
263254

1-[1-(4-Chlorophenylsulfonyl)piperidin-4-ylcarbonyl]-4-(4-pyrimidinyl)piperazine



C20-H24-Cl-N5-O3-S; Mol wt: 449.95

ACTION – Agent for the treatment of hypercholesterolemia and atherosclerosis that inhibits cholesterol biosynthesis due to its ability to inhibit lanosterol synthase (IC_{50} = 81 nM in rat liver microsome preparations). *In vivo* activity was demonstrated in rats, giving 72% inhibition of cholesterol biosynthesis at a dose of 5 mg/kg p.o. A representative compound within a series of substituted pyrimidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
265036	Pr	Br	H	C ₂₃ H ₃₀ BrN ₅ O ₃ S
265037	Et	Br	H	C ₂₂ H ₂₈ BrN ₅ O ₃ S
265039	Me	Br	H	C ₂₁ H ₂₆ BrN ₅ O ₃ S
265040	Me	Cl	H	C ₂₁ H ₂₆ ClN ₅ O ₃ S
265041	Me	F	H	C ₂₁ H ₂₆ FN ₅ O ₃ S
265042	Me	F	Cl	C ₂₁ H ₂₅ ClFN ₅ O ₃ S
265043	Me	H	F	C ₂₁ H ₂₆ FN ₅ O ₃ S

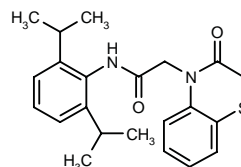
SOURCE – Zeneca.

REFERENCES

1. Brown, G.R. et al. (Zeneca, Ltd.) *Substd. pyrimidine derivs. and their pharmaceutical use.* WO 9806705.

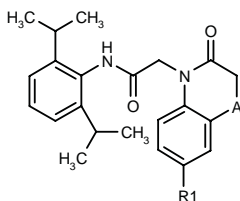
264334

N-(2,6-Diisopropylphenyl)-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-4-yl)acetamide

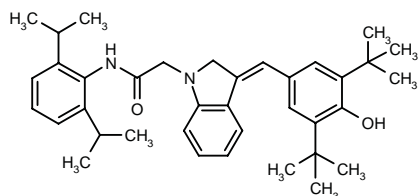


C22-H26-N2-O2-S; Mol wt: 382.52

ACTION – Hypolipidemic and antiatherosclerotic agent with ACAT-inhibitory activity (IC_{50} = 1.2 μ M using enzyme from rat hepatic microsomes), shown to inhibit cholesterol esterification *in vitro* in murine macrophages (IC_{50} = 2.4 μ M). Other compounds from this series of acetamide derivatives include the following:



Compound	R1	A	Formula
265551	H	O	C ₂₂ H ₂₆ N ₂ O ₃
265552	F	CH ₂	C ₂₃ H ₂₇ N ₂ O ₂



265553: C37-H48-N2-O2

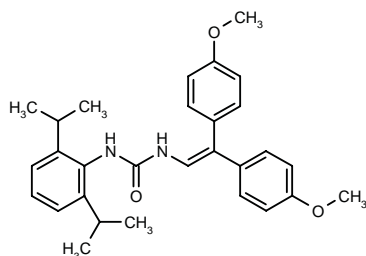
SOURCE – Sanwa.

REFERENCES

1. Suzuki, T. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Acetamide derivs. and their use*. JP 98095766.

264365

N-[2,2-Bis(4-methoxyphenyl)vinyl]-*N'*-(2,6-diisopropylphenyl)urea



C29-H34-N2-O3; Mol wt: 458.60

ACTION – Antiatherosclerotic agent, an ACAT inhibitor that exhibits higher potency against enzyme from murine macrophage J774 cells (77.82 ± 4.00% inhibition at 100 nM) than from rat liver microsomes (7.87 ± 9.26% inhibition at 100 nM).

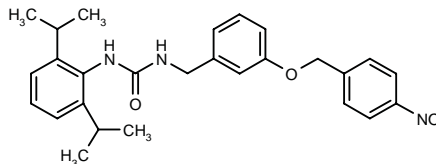
SOURCE – SS Pharm.

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1. Kanamaru, Y. et al. (SS Pharm. Co., Ltd.) *Substd. vinyl urea derivs. and medicines containing the same*. JP 98109969.

265150

N-(2,6-Diisopropylphenyl)-*N'*-[3-(4-nitrobenzyloxy)benzyl]urea



C27-H31-N3-O4; Mol wt: 461.56

ACTION – Antiarteriosclerotic agent that selectively inhibits ACAT in macrophages compared to ACAT from liver microsomes.

SOURCE – SS Pharm.

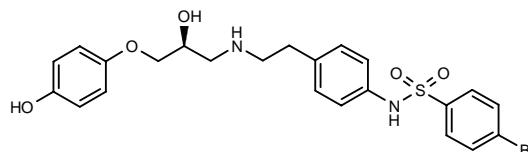
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ANTIOBESITY DRUGS

263737

(*S*)-4-Bromo-*N*-[4-[2-[2-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl]phenyl]benzenesulfonamide



C23-H25-Br-N2-O5-S; Mol wt: 521.42

ACTION – Potent and selective β_3 -adrenoceptor agonist with > 200-fold selectivity for β_3 - over β_1 - and β_2 -adrenoceptors; agonist activity at β_3 -adrenoceptors was demonstrated by increases in cAMP in CHO cells expressing cloned human β_3 -adrenoceptors (EC_{50} = 0.77 nM) but not in cells expressing cloned human β_1 - or β_2 -adrenoceptors (EC_{50} = 340 nM for β_1 ; 0% activity at 1000 nM for β_2), and it gave IC_{50} values for β_1 - and β_2 -adrenoceptor binding of 510 and 180 nM, respectively. Potentially useful as an antiobesity drug.

SOURCE – Merck & Co.

REFERENCES

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2. Weber, A.E. et al. *Potent, selective benzenesulfonamide agonists of the human β_3 adrenergic receptor*. Bioorg Med Chem Lett 1998, 8(9): 1101.

ORLISTAT

Rec INN; USAN

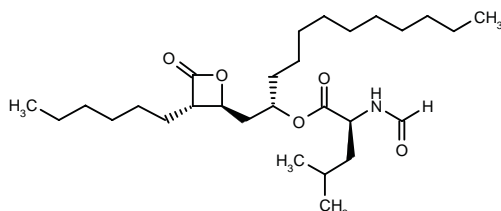
110823**N-Formyl-L-leucine 1(S)-[(2S,3S)-3-hexyl-4-oxooxetanylmethyl]dodecyl ester**

Orlipastat (former INN)

Ro-18-0647

Ro-18-0647/002

Tetrahydrolipstatin*



C29-H53-N-O5; Mol wt: 495.74

ACTION – Nonsystemic antiobesity agent, a potent, specific and long-acting inhibitor of gastrointestinal lipases.

INDICATION – Long-term treatment of significantly obese patients, including patients with risk factors associated with obesity, in conjunction with a mildly hypocaloric diet.

PRESENTATION – Capsules, 120 mg.

PROPRIETARY NAME – *Xenical* (NZ).

SOURCE – Roche.

RECENT REFERENCES

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2. Davidson, M. *A 2-year US multicentre study of orlistat in the treatment of obesity.* Eur Heart J 1997, 18(Suppl.): Abst 937.
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12. Nosed, G. and Fragiaco, C. *Improved cardiovascular risk profile in obese subjects after long-term treatment with orlistat.* 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 10.
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19. *FDA advisory committee reaches a stand-off on orlistat recommendation.* Prous Science Daily Essentials March 16, 1998.

20. *FDA advisory committee unanimously recommends Xenical® (orlistat) for weight loss.* Roche Press Release 1997, May 14.

21. *FDA issues approvable letter for Roche's novel antiobesity Rx.* Prous Science Daily Essentials May 14, 1998.

22. *Orlistat launch.* Roche Company Communication 1998, June 19.

23. *Orlistat reaches first market.* Prous Science Daily Essentials June 19, 1998.

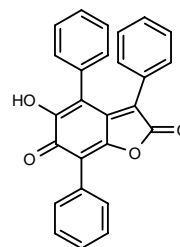
24. *Roche resubmits NDA for Xenical.* Prous Science Daily Essentials November 17, 1997.

25. *Roche withdraws NDA for orlistat.* Prous Science Daily Essentials August 28, 1997.

26. *Xenical scheduled for FDA advisory panel review.* Prous Science Daily Essentials February 26, 1998.

MONOGRAPH – Prous, J. et al. *Orlistat.* Drugs Fut 1994, 19(11): 1003.

*See **Lipstatin** Drug Data Rep 1985, 7(11): 784.

**TREATMENT OF GOUT AND
HYPERURICEMIA****264496****5-Hydroxy-3,4,7-triphenyl-2,6-benzofurandione**

C26-H16-O4; Mol wt: 392.41

Greenish microcrystals, m.p. 137-8 °C.

ACTION – Xanthine oxidase inhibitor extracted from the fungus *Peniophora sanguinea* that inhibits the production of superoxide anion radicals; it inhibited chemiluminescence induced by xanthine oxidase and enhanced by lucigenin ($IC_{50} = 1.276 \mu M$) with efficacy comparable to allopurinol ($IC_{50} = 2.35 \mu M$). It exhibited cytotoxic activity against mouse fibroblast L-929 cells, human leukemia K-562 cells and HeLa cells ($IC_{50} = 2.8, 3.8$ and $14.1 \mu g/ml$, respectively). Potentially useful in the treatment of gout, stroke and cardiovascular disorders.

SOURCES – Hans-Knöll-Inst. Nat. Prod. Res., Jena (DE); ICI Specialities; Jena Univ., Jena (DE); Univ. Nottingham, Nottingham (GB).

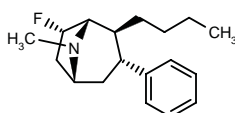
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TREATMENT OF POISONING AND
DRUG DEPENDENCY

265752

(±)-(2β,3α,7α)-2-Butyl-7-fluoro-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane



C18-H26-F-N; Mol wt: 275.41

Pale yellow oil.

ACTION – Dopamine transporter ligand that inhibits mazindol binding in rat striatum with a K_i of 0.20 μ M and dopamine reuptake into synaptosomes with a K_i of 0.68 μ M. Potentially useful in the treatment of cocaine abuse.

SOURCES – Georgetown Univ. Med. Cent., Washington, D.C. (US); Univ. Texas, Galveston, TX (US).

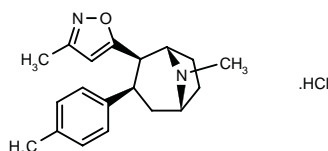
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RTI-171

263278

8-Methyl-2β-(3-methylisoxazol-5-yl)-3β-(4-methylphenyl)-8-azabicyclo[3.2.1]octane hydrochloride



C19-H24-N2-O.HCl; Mol wt: 332.87

ACTION – Agent with high affinity for cocaine receptors in the brain, particularly those associated with dopamine transporter sites, as demonstrated in binding assays by K_i values of 0.93 ± 0.09 , 254 ± 31 and 3818 ± 346 nM, respectively, for dopamine, norepinephrine and 5-HT transporters. Potentially useful in the treatment of drug addiction, depression, anorexia and neurodegenerative diseases, and as an imaging agent in the diagnosis of these conditions.

SOURCE – Research Triangle Inst.

REFERENCES

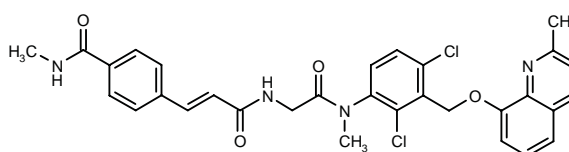
1. Kuhar, M.J. et al. (Research Triangle Inst.) Cocaine receptor binding ligands. WO 9807427.

PHARMACOLOGICAL TOOLS

FR-165649

265029

N^1 -[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-phenyl]- N^1 -methyl- N^2 -[4-(N -methylcarbamoyl)cinnamoyl]glycinamide



C31-H28-Cl2-N4-O4; Mol wt: 591.49

ACTION – Potent, nonpeptide bradykinin B_2 receptor antagonist structurally similar to the agonist FR-190997, with IC_{50} values of 0.47 and 1.6 nM, respectively, in guinea pig ileum membranes and human lung fibroblast IMR-90 cells. In functional studies, it had no agonist effect, whereas it antagonized bradykinin-induced contractions in guinea pig ileum ($pA_2 = 9.2 \pm 0.1$) and it antagonized the bradykinin-induced increase in phosphatidylinositol hydrolysis in IMR-90 cells. Potentially useful as a tool for elucidating the pathophysiological role of bradykinin.

SOURCE – Fujisawa.

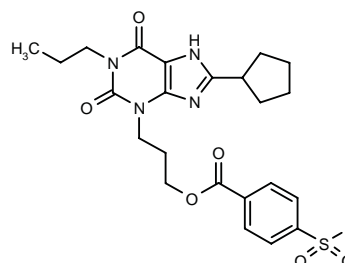
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FSCPX

233326

4-Fluorosulfonylbenzoic acid 3-(8-cyclopentyl-1-propyl-xanthin-3-yl)propyl ester



C23-H27-F-N4-O6-S; Mol wt: 506.55

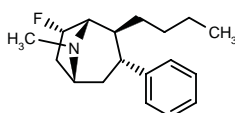
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TREATMENT OF POISONING AND
DRUG DEPENDENCY

265752

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C18-H26-F-N; Mol wt: 275.41

Pale yellow oil.

ACTION – Dopamine transporter ligand that inhibits mazindol binding in rat striatum with a K_i of 0.20 μ M and dopamine reuptake into synaptosomes with a K_i of 0.68 μ M. Potentially useful in the treatment of cocaine abuse.

SOURCES – Georgetown Univ. Med. Cent., Washington, D.C. (US); Univ. Texas, Galveston, TX (US).

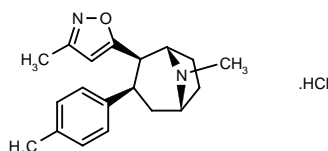
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1. Prakash, K.R.C. et al. Synthesis and biological activity of new 6- and 7-substituted 2β-butyl-3-phenyltropanes as ligands for the dopamine transporter. Med Chem Res 1998, 8(1-2): 43.

RTI-171

263278

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SOURCE – Research Triangle Inst.

REFERENCES

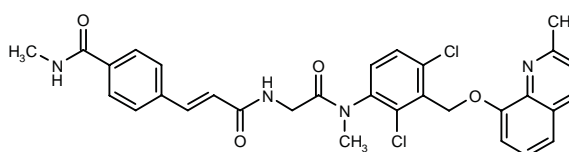
1. Kuhar, M.J. et al. (Research Triangle Inst.) Cocaine receptor binding ligands. WO 9807427.

PHARMACOLOGICAL TOOLS

FR-165649

265029

N^1 -[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-phenyl]- N^1 -methyl- N^2 -[4-(N -methylcarbamoyl)cin-namoyl]glycinamide



C31-H28-Cl2-N4-O4; Mol wt: 591.49

ACTION – Potent, nonpeptide bradykinin B_2 receptor antagonist structurally similar to the agonist FR-190997, with IC_{50} values of 0.47 and 1.6 nM, respectively, in guinea pig ileum membranes and human lung fibroblast IMR-90 cells. In functional studies, it had no agonist effect, whereas it antagonized bradykinin-induced contractions in guinea pig ileum ($pA_2 = 9.2 \pm 0.1$) and it antagonized the bradykinin-induced increase in phosphatidylinositol hydrolysis in IMR-90 cells. Potentially useful as a tool for elucidating the pathophysiological role of bradykinin.

SOURCE – Fujisawa.

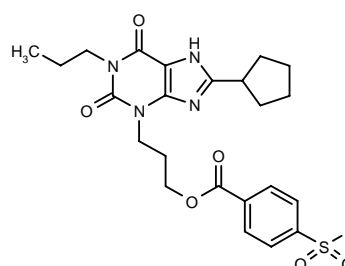
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FSCPX

233326

4-Fluorosulfonylbenzoic acid 3-(8-cyclopentyl-1-propyl-xanthin-3-yl)propyl ester



C23-H27-F-N4-O6-S; Mol wt: 506.55

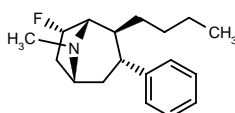
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TREATMENT OF POISONING AND DRUG DEPENDENCY

265752

(±)-(2β,3α,7α)-2-Butyl-7-fluoro-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane



C18-H26-F-N; Mol wt: 275.41

Pale yellow oil.

ACTION – Dopamine transporter ligand that inhibits mazindol binding in rat striatum with a K_i of 0.20 μ M and dopamine reuptake into synaptosomes with a K_i of 0.68 μ M. Potentially useful in the treatment of cocaine abuse.

SOURCES – Georgetown Univ. Med. Cent., Washington, D.C. (US); Univ. Texas, Galveston, TX (US).

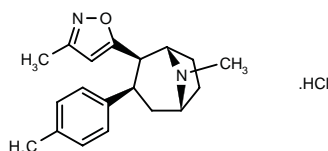
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RTI-171

263278

8-Methyl-2β-(3-methylisoxazol-5-yl)-3β-(4-methylphenyl)-8-azabicyclo[3.2.1]octane hydrochloride



C19-H24-N2-O.HCl; Mol wt: 332.87

ACTION – Agent with high affinity for cocaine receptors in the brain, particularly those associated with dopamine transporter sites, as demonstrated in binding assays by K_i values of 0.93 ± 0.09 , 254 ± 31 and 3818 ± 346 nM, respectively, for dopamine, norepinephrine and 5-HT transporters. Potentially useful in the treatment of drug addiction, depression, anorexia and neurodegenerative diseases, and as an imaging agent in the diagnosis of these conditions.

SOURCE – Research Triangle Inst.

REFERENCES

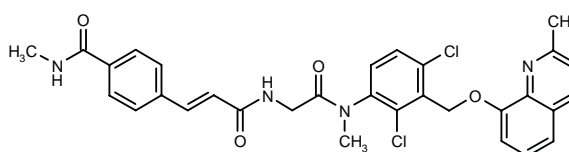
1. Kuhar, M.J. et al. (Research Triangle Inst.) Cocaine receptor binding ligands. WO 9807427.

PHARMACOLOGICAL TOOLS

FR-165649

265029

N^1 -[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-phenyl]- N^1 -methyl- N^2 -[4-(N -methylcarbamoyl)cin-namoyl]glycinamide



C31-H28-Cl2-N4-O4; Mol wt: 591.49

ACTION – Potent, nonpeptide bradykinin B_2 receptor antagonist structurally similar to the agonist FR-190997, with IC_{50} values of 0.47 and 1.6 nM, respectively, in guinea pig ileum membranes and human lung fibroblast IMR-90 cells. In functional studies, it had no agonist effect, whereas it antagonized bradykinin-induced contractions in guinea pig ileum ($pA_2 = 9.2 \pm 0.1$) and it antagonized the bradykinin-induced increase in phosphatidylinositol hydrolysis in IMR-90 cells. Potentially useful as a tool for elucidating the pathophysiological role of bradykinin.

SOURCE – Fujisawa.

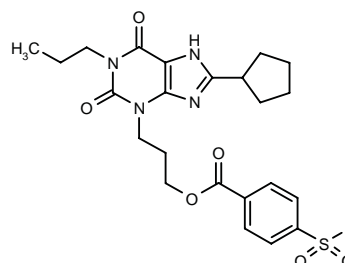
REFERENCES

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2. Asano, M. et al. Pharmacological characterization of a nonpeptide bradykinin B_2 receptor antagonist, FR165649, and agonist, FR190997. Brit J Pharmacol 1998, 124(3): 441.

FSCPX

233326

4-Fluorosulfonylbenzoic acid 3-(8-cyclopentyl-1-propyl-xanthin-3-yl)propyl ester



C23-H27-F-N4-O6-S; Mol wt: 506.55

ACTION – Selective and irreversible adenosine A₁ receptor antagonist with high affinity for adenosine A₁ receptors (IC₅₀ = 1.2, 8.8 and 8.6 nM, respectively, for displacement of [³H]-CPX binding in guinea pig brain, ventricle and atria membranes) and much lower affinity for the adenosine A_{2a} receptor (IC₅₀ = 135.8 nM for displacement of [³H]-CGS-21680 binding in guinea pig brain). It selectively antagonized cardiac adenosine A₁ receptor-mediated responses in an irreversible manner. It is suggested to have potential use in measuring adenosine receptor reserve.

SOURCE – Univ. Florida., Gainesville, FL (US).

REFERENCES

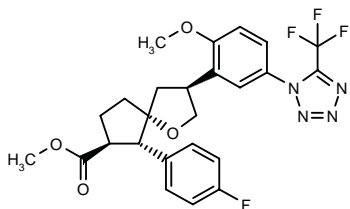
1. De Groote, M. et al. *FSCPX is an irreversible antagonist of both rat and human adenosine A1 receptors*. Drug Dev Res 1998, 43(1): Abst 39.
 2. Srinivas, M. et al. *An irreversible antagonist of the cardiac A1-adenosine receptor*. Circulation 1995, 92(8, Suppl.): Abst 1132.
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 4. Srinivas, M. et al. *A novel irreversible antagonist of the A1-adenosine receptor*. Mol Pharmacol 1996, 50(1): 196.
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

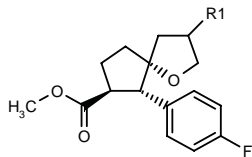
264865

(3*R**,5*S**,6*R**,7*R**)-6-(4-Fluorophenyl)-3-[2-methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]-1-oxaspiro[4.4]-nonane-7-carboxylic acid methyl ester



C25 H24 F4 N4 O4; Mol wt: 520.4806

ACTION – Agent for the treatment of pain, inflammation, migraine, asthma, gastrointestinal disorders and CNS disorders, a tachykinin, especially substance P (NK₁ receptor), antagonist. Within this series of specifically claimed spiroethercycloalkyl derivatives, the following are also included:



Compound	R1	Isomer	Formula
266070	2-MeO-5-(5-CF3-1-tetrazolyl)-3-Pyr		C ₂₄ H ₂₃ F ₄ N ₅ O ₄
266071	2-MeO-5-(5-CF3-1-tetrazolyl)-3-Pyr	3S	C ₂₄ H ₂₃ F ₄ N ₅ O ₄
266072	3-MeO-5-(5-CF3-1-tetrazolyl)-2-Pyr		C ₂₄ H ₂₃ F ₄ N ₅ O ₄
266073	3-MeO-6-(5-CF3-1-tetrazolyl)-2-Pyr	3S	C ₂₄ H ₂₃ F ₄ N ₅ O ₄
266074	5-(CF3O)-2,3-dihydro-7-benzofuryl		C ₂₅ H ₂₄ F ₄ O ₅
266075	1-Me-5-CF3-7-benzimidazolyl		C ₂₅ H ₂₄ F ₄ N ₂ O ₃

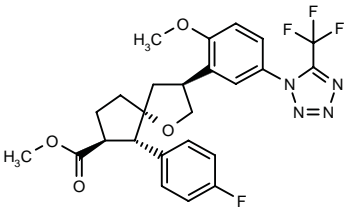
SOURCE – Merck & Co.

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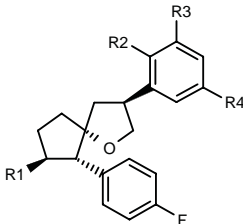
264885

(3*S*,5*R*,6*S*,7*S*)-6-(4-Fluorophenyl)-3-[2-methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]-1-oxaspiro[4.4]nonane-7-carboxylic acid methyl ester

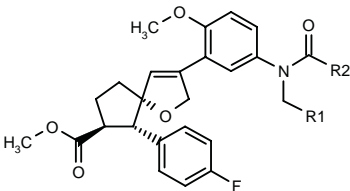


C25 H24 F4 N4 O4; Mol wt: 520.4806

ACTION – Agent for the treatment of pain, inflammation, migraine, emesis and asthma, a tachykinin, especially substance P (NK₁ receptor), antagonist. Within this series of specifically claimed spiroethercycloalkyl derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
266077	1-pyrrolidinyl-CH2	OMe	H	5-CF3-1-tetrazolyl	C ₂₈ H ₃₁ F ₄ N ₅ O ₂
266078	1-pyrrolidinyl-CH2	Me	F	5-CF3-1-tetrazolyl	C ₂₈ H ₃₀ F ₅ N ₅ O
266079	CO2Me	OMe	H	N(Me)Ac	C ₂₆ H ₃₀ FNO ₅



Compound	R1	R2	Formula
266080	H	Me	C ₂₆ H ₂₈ FNO ₅
266081	H	CF3	C ₂₆ H ₂₅ F ₄ NO ₅
266082	Me	Me	C ₂₇ H ₃₀ FNO ₅

SOURCE – Merck & Co.

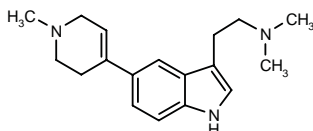
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ANTIMIGRAINE DRUGS

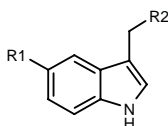
266174

N,N-Dimethyl-*N*-[2-[5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-3-yl]ethyl]amine



C18 H25 N3; Mol wt: 283.4165

ACTION – Antimigraine agent, a 5-HT_{1D}-like receptor agonist with an EC₅₀ value of 0.75 µM in the isolated rabbit saphenous vein assay compared to a value of 0.22 µM for sumatriptan. *In vivo*, compound was found to inhibit protein extravasation in a trigeminal stimulation assay in guinea pigs, indicating agonist activity at the 5-HT_{1D} and/or 5-HT_{1F} receptor. Other compounds from this series of indole derivatives include the following:



Compound	R1	R2	Formula
266903	1-cyclohexenyl	CH2N(Me)2	C ₁₈ H ₂₄ N ₂
266904	2-THP	CH2N(Me)2	C ₁₇ H ₂₄ N ₂ O
266906	cyclohexyl	CH2N(Me)2	C ₁₈ H ₂₆ N ₂
266907	1-(<i>t</i> -BuOCO)-4-Pip	1-Me-2(S)-pyrrolidinyl	C ₂₄ H ₃₅ N ₃ O ₂
266908	5,6-dihydro-4 <i>H</i> -2-pyranyl	1-Me-2(S)-pyrrolidinyl	C ₁₉ H ₂₄ N ₂ O

SOURCE – Allelix.

REFERENCES

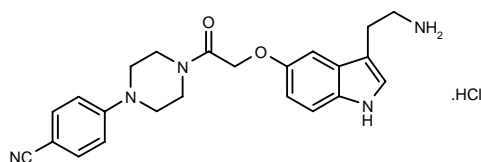
1. Slassi, A. et al. (Allelix Biopharmaceuticals Inc.) 5-Cyclo indole cpds. as 5-HT_{1D} receptor ligands. WO 9823587.

F-11356*

266330

260121 (as mesylate)

4-[4-[2-[3-(2-Aminoethyl)-1*H*-indol-5-yloxy]acetyl]-piperazin-1-yl]benzonitrile hydrochloride



C23 H25 N5 O2 . HCl; Mol wt: 439.9444

ACTION – Potent, selective, centrally and orally active 5-HT_{1B/1D} receptor agonist with high affinity for human and nonhuman 5-HT_{1B} and 5-HT_{1D} receptor subtypes (pK_i = 9.32 and 10.32, respectively), 50-fold lower affinity for 5-HT_{1A} receptors (pK_i = 7.60) and no affinity for other neurotransmitter and neuropeptide receptors and binding sites. Similar to 5-HT, the compound inhibited forskolin-stimulated cAMP formation in CHO-K1 cells expressing recombinant 5-HT_{1B} or 5-HT_{1D} receptors (pEC₅₀ = 8.90-9.81), being much less potent in cells expressing recombinant human 5-HT_{1A} receptors (pEC₅₀ = 5.94). F-11356 was also shown to be as potent as 5-HT in the agonist-stimulated [³⁵S]-GTPγS binding assay in C6-glia cell membrane preparations (pA₂ = 6.81-8.90). Title compound was equipotent to 5-HT and more potent than sumatriptan in producing contractile responses in isolated rabbit saphenous vein rings (pEC₅₀ = 7.1, 7.2 and 5.8 for F-11356, 5-HT and sumatriptan, respectively). The 5-HT_{1B/1D} antagonist GR-127935 concentration-dependently antagonized the contractile responses evoked by F-11356 in a competitive manner. The compound administered i.v. decreased carotid blood flow in anesthetized pigs (ED₅₀ = 0.53 µg/kg) and it produced a dose-dependent and long-lasting decrease in carotid blood flow following oral administration in anesthetized dogs, without undesirable side effects. Central activity was indicated by its ability to induce hypothermia in guinea pigs (ED₅₀ = 1.58 mg/kg p.o. vs. 8.25-12.3 mg/kg p.o. for zolmitriptan, naratriptan and rizatriptan). Potentially useful for the treatment of migraine.

SOURCE – Pierre Fabre.

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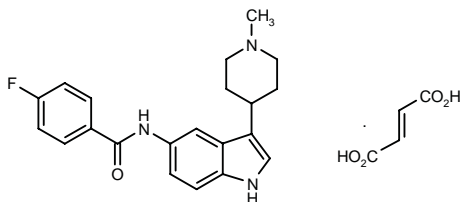
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2. Halazy, S. et al. (Pierre Fabre Médicament) Indole-derived azyloperazines as ligands for 5HT₁-like receptors 5HT_{1B} and 5HT_{1D}. EP 729455, FR 2712591, JP 97505072, US 5726177, WO 9514004.
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*Identified compound 260121 Drug Data Report 1998, 020(04): 0292.

LY-334370

265976

4-Fluoro-*N*-[3-(1-methyl-4-piperidiny)-1*H*-indol-5-yl]-benzamide fumarate



C21 H22 F N3 O . C4 H4 O4; Mol wt: 467.4944

ACTION – Potent and selective 5-HT_{1F} receptor agonist with high affinity for this receptor ($K_i = 1.6$ nM; $pK_i = 8.78$), significant affinity for the 5-HT_{1A} receptor ($K_i = 11.9$ nM) and much lower affinity for 5-HT_{1B} ($pK_i = 6.87$) and 5-HT_{1D} receptors ($pK_i = 6.86$) in binding studies. In functional studies of its ability to inhibit forskolin-stimulated adenylate cyclase in cloned cells, it was much more potent in activating the 5-HT_{1F} receptor ($EC_{50} = 1.6$ nM) than the 5-HT_{1A} receptor ($EC_{50} = 1825$ nM). It was devoid of vasoconstrictor properties on the rabbit saphenous vein ($pEC_{50} < 4.00$), but potently inhibited neurogenic dural inflammation in rats ($ID_{50} = 20$ pg/kg i.v., 30 pg/kg p.o.) and guinea pigs ($ID_{50} = 30$ pg/kg i.v., 45 pg/kg p.o.); it was also effective following s.c. and sublingual administration, and in guinea pigs pretreated with 200 pg/kg p.o., a dose near the ID_{100} , it inhibited neurogenic dural inflammation for at least 16 h. LY-334370 displayed a low potential for toxicity in studies in several animal species. It is currently in clinical trials for acute migraine.

SOURCES – Lilly; Synaptic.

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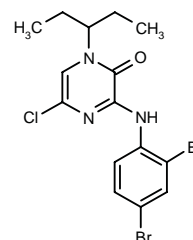
21. Lilly and Synaptic enter late-stage trials with antimigraine agent. Daily Essentials 1998, Sept 7.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

263842

5-Chloro-3-(2,4-dibromophenylamino)-1-(1-ethylpropyl)-pyrazin-2(1*H*)-one



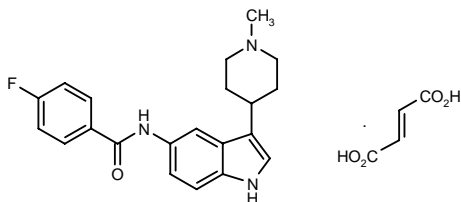
C15 H16 Br2 Cl N3 O; Mol wt: 449.5724

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist claimed for the treatment of affective disorders, anxiety, depression, posttraumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disorders, eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders or fertility disorders. Other specifically claimed compounds from this series of pyrazinones and triazinones include the following:

LY-334370

265976

4-Fluoro-*N*-[3-(1-methyl-4-piperidiny)-1*H*-indol-5-yl]-benzamide fumarate



C₂₁ H₂₂ F N₃ O₄; Mol wt: 467.4944

ACTION – Potent and selective 5-HT_{1F} receptor agonist with high affinity for this receptor ($K_i = 1.6$ nM; $pK_i = 8.78$), significant affinity for the 5-HT_{1A} receptor ($K_i = 11.9$ nM) and much lower affinity for 5-HT_{1B} ($pK_i = 6.87$) and 5-HT_{1D} receptors ($pK_i = 6.86$) in binding studies. In functional studies of its ability to inhibit forskolin-stimulated adenylate cyclase in cloned cells, it was much more potent in activating the 5-HT_{1F} receptor ($EC_{50} = 1.6$ nM) than the 5-HT_{1A} receptor ($EC_{50} = 1825$ nM). It was devoid of vasoconstrictor properties on the rabbit saphenous vein ($pEC_{50} < 4.00$), but potently inhibited neurogenic dural inflammation in rats ($ID_{50} = 20$ pg/kg i.v., 30 pg/kg p.o.) and guinea pigs ($ID_{50} = 30$ pg/kg i.v., 45 pg/kg p.o.); it was also effective following s.c. and sublingual administration, and in guinea pigs pretreated with 200 pg/kg p.o., a dose near the ID_{100} , it inhibited neurogenic dural inflammation for at least 16 h. LY-334370 displayed a low potential for toxicity in studies in several animal species. It is currently in clinical trials for acute migraine.

SOURCES – Lilly; Synaptic.

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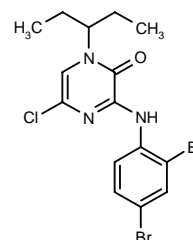
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PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

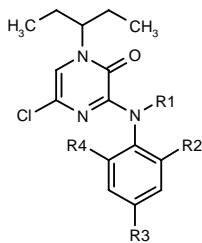
263842

5-Chloro-3-(2,4-dibromophenylamino)-1-(1-ethylpropyl)-pyrazin-2(1*H*)-one



C₁₅ H₁₆ Br₂ Cl N₃ O; Mol wt: 449.5724

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist claimed for the treatment of affective disorders, anxiety, depression, posttraumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disorders, eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders or fertility disorders. Other specifically claimed compounds from this series of pyrazinones and triazinones include the following:



Compound	R1	R2	R3	R4	Formula
267045	H	Br	i-Pr	H	C ₁₈ H ₂₃ BrClN ₃ O
267046	Et	Br	Br	H	C ₁₇ H ₂₀ Br ₂ ClN ₃ O
267047	Et	Br	i-Pr	H	C ₂₀ H ₂₇ BrClN ₃ O
267048	H	Me	Me	Me	C ₁₈ H ₂₄ ClN ₃ O
267049	Et	Me	Me	Me	C ₂₀ H ₂₈ ClN ₃ O
267050	H	OMe	Br	OMe	C ₁₇ H ₂₁ BrClN ₃ O ₃

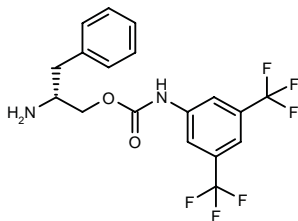
SOURCE – DuPont Pharm.

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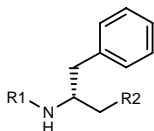
264872

N-[3,5-Bis(trifluoromethyl)phenyl]carbamic acid 2(*R*)-amino-3-phenylpropyl ester



C18 H16 F6 N2 O2; Mol wt: 406.3244

ACTION – Agent for the treatment of CNS disorders such as anxiety, depression, cognition impairment, pain and alcohol abuse, a neuropeptide Y₁ (NPY₁) receptor agonist, as demonstrated in a binding assay (IC₅₀ = 1.0 μM against [¹²⁵I]-NPY binding to NPY₁ receptors in human neuroblastoma SK-N-MC cells). Agonist activity was demonstrated by inhibition of the forskolin-induced increase in cAMP levels in SK-N-MC cells. It exhibited some anxiolytic activity in a rat conflict assay, but was inactive in a monkey conflict assay, against pentylenetetrazol-induced convulsions in mice, in a rat behavioral model of trait anxiety and in tests for muscle relaxant and hypnotic/sedative effects. Other compounds from this series of phenylalaninol derivatives include the following:



Compound	R1	R2	Formula
265815	4-(NH ₂ CH ₂)- -PhCO	3,5-(CF ₃) ₂ -PhNHCOO	C ₂₆ H ₂₃ F ₆ N ₃ O ₃
265816	H	3,4-(Cl) ₂ -PhNHCOO	C ₁₆ H ₁₆ Cl ₂ N ₂ O ₂
265817	H	3,5-(CF ₃) ₂ -PhNHCONH	C ₁₈ H ₁₇ F ₆ N ₃ O
265818	H	3,5-(CF ₃) ₂ -PhCH ₂ CONH	C ₁₉ H ₁₈ F ₆ N ₂ O
265819	H	3,5-(CF ₃) ₂ -PhCONH	C ₁₈ H ₁₆ F ₆ N ₂ O

SOURCE – Ortho-McNeil.

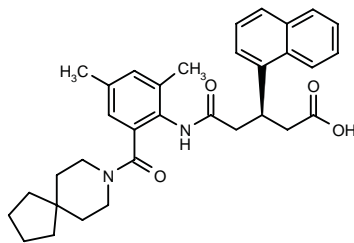
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CR-2945*

261157
247719* (undefined stereochemistry)

(*R*)-*N*-[2-(8-Azaspiro[4.5]decan-8-ylcarbonyl)-4,6-dimethylphenyl]-3-(1-naphthyl)glutaramic acid



C33 H38 N2 O4; Mol wt: 526.6732

ACTION – Anxiolytic agent, a potent and selective, nonpeptide CCK_B receptor antagonist (K_i = 2.3 nM for CCK_B receptors in rat cerebral cortex vs. 20,700 nM for CCK_A receptors in rat pancreatic acini; CCK_A/CCK_B = 9000); it also dose-dependently inhibited [¹²⁵I]-BH-CCK-8 binding *in vivo* in rats with ID₅₀ values of 10.9 mg/kg i.v. and 13.5 mg/kg s.c. Anxiolytic activity was demonstrated in rodent tests of anxiety, i.e., the elevated plus-maze in rats (0.01-30 mg/kg p.o.), the light/dark box in mice (0.1-1 mg/kg i.p.), the elevated zero-maze in rats (0.1-10 mg/kg s.c. or p.o.) and the rat water-drinking conflict test (0.1-10 mg/kg p.o.). No signs of sedation or ataxia were detected even at the highest doses tested and no induction of tolerance or withdrawal anxiety was observed after repeated administration.

SOURCE – Rotta.

REFERENCES

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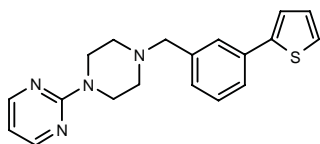
*Identified compound **261157** Drug Data Report 1998, 020(04): 0295.

*Drug Data Report 1997, 019(05): 0433.

ANTIPSYCHOTIC DRUGS

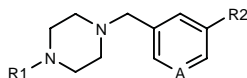
263840

1-(2-Pyrimidinyl)-4-[3-(2-thienyl)benzyl]piperazine



C₁₉ H₂₀ N₄ S; Mol wt: 336.4610

ACTION – Agent with selective affinity for dopamine D₄ receptors relative to D₂ and D₃ receptors, also reported to behave as a 5-HT_{1A} agonist and 5-HT reuptake inhibitor. Potentially useful for the treatment or prevention of schizophrenia, anxiety, depression, obsessive disorders, tardive dyskinesia, Parkinson's disease, nausea and gastrointestinal disorders. Other specifically claimed compounds from this series of substituted piperazines include the following:



Compound	R1	R2	A	Formula
266016	2-pyrimidinyl	4-F-Ph	N	C ₂₀ H ₂₀ FN ₅
266017	4-CN-Ph	Ph	CH	C ₂₄ H ₂₃ N ₃
266018	4-Cl-Ph	4-F-Ph	N	C ₂₂ H ₂₁ ClFN ₃
266019	2-pyrimidinyl	3-F-Ph	CH	C ₂₁ H ₂₁ FN ₄
266020	2-pyrimidinyl	3-thienyl	N	C ₁₈ H ₁₉ N ₅ S

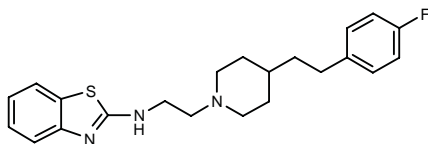
SOURCE – Merck KGaA.

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264411

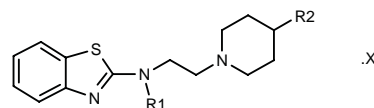
N-(2-Benzothiazolyl)-*N*-[2-[4-(4-fluorophenyl)ethyl]piperidin-1-yl]ethylamine



C₂₂ H₂₆ F N₃ S; Mol wt: 383.5324

ACTION – Dopamine D₄ receptor ligand with neuroprotective activity, as demonstrated by 48% reduction of infarct volume in a rat model of permanent focal ischemia when given at 1 mg/kg i.v. at 10 min and 1.5, 3 and 6 h postocclusion. Potentially useful for the treatment of psychoses, anxiety, panic attacks, phobia, depression, cognitive disorders, as well as a neuroprotectant. A representative compound from a series

of *N*-(benzothiazol-2-yl)piperidine-1-ethanamine derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
266021	H	4-F-PhCH ₂	oxalate	C ₂₁ H ₂₄ FN ₃ S.C ₂ H ₂ O ₄
266022	Me	CH ₂ Ph	oxalate	C ₂₂ H ₂₇ N ₃ S.C ₂ H ₂ O ₄
266023	H	Ph		C ₂₀ H ₂₃ N ₃ S

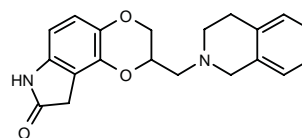
SOURCE – Synthélabo.

REFERENCES

1. Dargazanli, G. et al. (Synthélabo) *N*-(Benzothiazol-2-yl) piperidine-1-ethanamine derivs., their preparation and application in therapeutics. WO 9814444.

264848

2-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)-2,3,8,9-tetrahydro-7*H*-1,4-dioxino[2,3-*e*]indol-8-one



C₂₀ H₂₀ N₂ O₃; Mol wt: 336.3890

ACTION – Antipsychotic agent, a dopamine autoreceptor agonist that also shows a partial agonist effect at postsynaptic dopamine D₂ receptors, as demonstrated in a binding assay using rat striatal brain preparations and [³H]-quinpirole as the radioligand (IC₅₀ = 0.35 nM). Compound produced functional antagonism of dopamine receptors *in vivo*, as demonstrated by its ability to reduce mouse locomotor activity with an ED₅₀ value of < 5 mg/kg s.c. A specifically claimed compound within a series of 2,3,8,9-tetrahydro-7*H*-1,4-dioxino[2,3-*e*]indol-8-one derivatives.

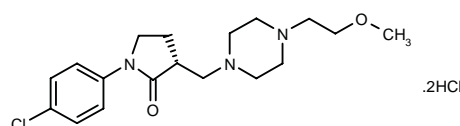
SOURCE – American Home Products.

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265151

1-(4-Chlorophenyl)-3-(*R*)-[4-(2-methoxyethyl)piperazin-1-ylmethyl]pyrrolidin-2-one dihydrochloride



C₁₈ H₂₆ Cl N₃ O₂ . 2 HCl; Mol wt: 424.7972

ACTION – Antipsychotic agent, a σ -receptor antagonist with affinity for σ_1 -receptors ($K_i = 72$ nM using [3 H]-(+)-pentazocine as the radioligand in guinea pig brain preparations) and devoid of affinity for dopamine D_2 receptors. *In vivo*, compound blocked head weaving induced by the σ -receptor agonists SK&F-10047 and phencyclidine in mice, with ED_{50} values of 0.77 and 0.75 mg/kg p.o. respectively; these effects are indicative of potent and long-lasting ($ED_{50} = 3.19$ mg/kg at 4 h for anti-SK&F-10047 effect) *in vivo* antipsychotic activity. Compound was highly effective in a methamphetamine-induced reverse tolerance model in the rat, and does not exhibit extrapyramidal side effects.

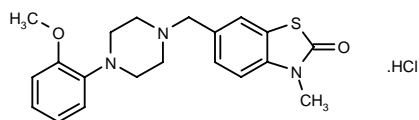
SOURCE – Mitsui Chem.

REFERENCES

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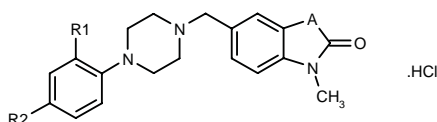
265156

6-[4-(2-Methoxyphenyl)piperazin-1-ylmethyl]-3-methylbenzothiazolin-2-one hydrochloride



C20 H23 N3 O2 S . HCl; Mol wt: 405.9476

ACTION – Antipsychotic agent with potent and selective affinity for dopamine D_4 receptors; in a binding assay, it exhibited a K_b value of 2.39 ± 1.10 nM when tested for its affinity for human dopamine D_4 receptors, whereas its affinity for 5-HT $_{1A}$ and dopamine D_2 receptors was at least 100 times lower. Low acute toxicity was observed, no deaths occurring after administration of 650 mg/kg p.o. to mice. Within this series of specifically claimed heterocyclic aminomethyl derivatives, the following are also included:



Compound	R1	R2	A	Formula
265864	F	H	S	C ₁₉ H ₂₀ FN ₃ OS.HCl
265865	H	Cl	O	C ₁₉ H ₂₀ ClN ₃ O ₂ .HCl

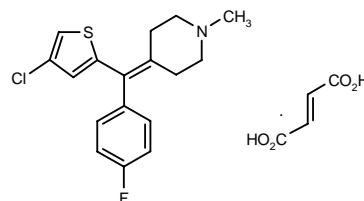
SOURCE – ADIR.

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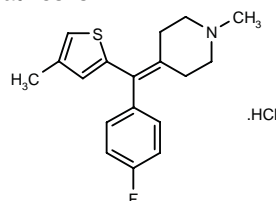
265490

4-[1-(4-Chlorothiophen-2-yl)-1-(4-fluorophenyl)methylene]-1-methylpiperidine fumarate



C17 H17 Cl F N S . C4 H4 O4; Mol wt: 437.9169

ACTION – Antipsychotic agent that exhibits no cataleptic effect and is thus expected to be devoid of extrapyramidal side effects. Antipsychotic activity was tested in the apomorphine climbing test in mice, where it gave ED_{50} values of 0.6 mg/kg s.c. and 5 mg/kg p.o. When tested for its ability to induce catalepsy in rats, compound gave an $ED_{50} > 50$ mg/kg compared to an ED_{50} value of 4.8 mg/kg for chlorpromazine. Another compound from this series of piperidine derivatives is:



266664: C18 H20 F N S.HCl

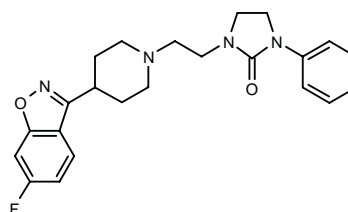
SOURCE – Akzo Nobel.

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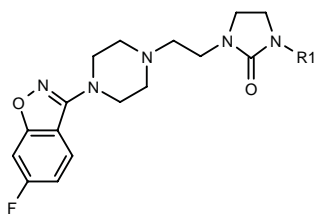
266085

1-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-3-phenylimidazolidin-2-one



C23 H25 F N4 O2; Mol wt: 408.4745

ACTION – Agent for the treatment of a variety of disorders including schizophrenia, anxiety and depression that is devoid of extrapyramidal side effects, a 5-HT $_{2A}$ receptor ($K_i < 10$ nM), α_1 -adrenoceptor ($K_i < 10$ nM) and dopamine D_4 receptor antagonist with at least 10-fold selectivity for D_4 relative to D_2 receptors ($K_i = 5$ nM or less for D_4 vs. 50 nM or more for D_2). *In vivo*, compound proved active in the apomorphine-induced climbing test in mice ($ID_{50} = 0.22$ mg/kg s.c.), in an active avoidance test in rats ($ID_{50} = 0.88$ mg/kg s.c.) and in a test measuring antiaggressive activity in isolated mice ($ID_{50} = 0.18$ mg/kg s.c.). When tested for its ability to induce catalepsy in rats, it was much less active than haloperidol or risperidone. Other specifically claimed compounds from this series of benzisoxazole derivatives include the following:



Compound	R1	Formula
266145	i-Pr	C ₁₉ H ₂₆ FN ₅ O ₂
266146	Et	C ₁₈ H ₂₄ FN ₅ O ₂

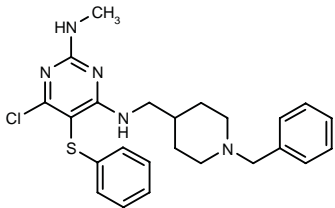
SOURCE – ADIR.

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266254

4-(1-Benzylpiperidin-4-ylmethylamino)-6-chloro-2-(methylamino)-5-(phenylsulfanyl)pyrimidine



C24 H28 Cl N5 S; Mol wt: 454.0392

ACTION – Agent for the treatment of neuropsychological disorders such as schizophrenia, mania, depression, Parkinson’s disease, substance abuse and Alzheimer’s disease, a dopamine D₄ receptor antagonist reported to possess negligible affinity for α₁-adrenoceptors.

SOURCE – Sumitomo.

REFERENCES

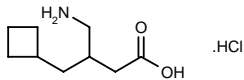
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

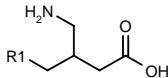
264870

3-(Aminomethyl)-4-cyclobutylbutyric acid hydrochloride



C9 H17 N O2 . HCl; Mol wt: 207.6992

ACTION – Agent for the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic disorders, pain, inflammation and gastrointestinal disorders, an analog of gabapentin with good binding affinity for the Ca²⁺ channel α2-δ subunit (IC₅₀ = 0.407 μM against [³H]-gabapentin binding to the α2-δ subunit derived from porcine brain tissue vs. 0.10-0.12 μM for gabapentin). Within this series of substituted γ-aminobutyric acids, the following are also specifically claimed:



Compound	R1	Formula
266117	cyclohexyl	C ₁₁ H ₂₁ NO ₂
266118	CH2Ph	C ₁₂ H ₁₇ NO ₂
266119	CH2SCH2Ph	C ₁₃ H ₁₉ NO ₂ S
266120	4-Br-PhCH2SCH2	C ₁₃ H ₁₈ BrNO ₂ S
266121	2,4-(Cl)2-PhCH2SCH2	C ₁₃ H ₁₇ Cl ₂ NO ₂ S
266122	4-NH2-PhCH2OCH2	C ₁₃ H ₂₀ N ₂ O ₃
266123	4-CF3-PhSCH2	C ₁₃ H ₁₆ F ₃ NO ₂ S
266124	4-Me-PhSCH2	C ₁₃ H ₁₉ NO ₂ S
266125	4-Cl-PhCH2CH2S	C ₁₃ H ₁₈ ClNO ₂ S
266126	3,4-(Cl)2-PhCH2CH2S	C ₁₃ H ₁₇ Cl ₂ NO ₂ S
266127	4-Me-PhCH2S	C ₁₃ H ₁₉ NO ₂ S
266128	4-Br-PhS	C ₁₁ H ₁₄ BrNO ₂ S
266129	3,4-(Cl)2-PhCH2S	C ₁₂ H ₁₅ Cl ₂ NO ₂ S
266130	cyclopropyl	C ₈ H ₁₆ ClNO ₂
266131	4-t-Bu-PhO	C ₁₅ H ₂₃ NO ₃

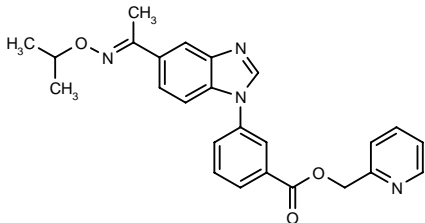
SOURCE – Warner-Lambert.

REFERENCES

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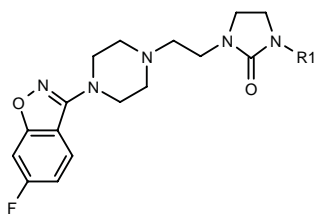
264879

3-[5-[1-(Isopropoxyimino)ethyl]benzimidazol-1-yl]benzoic acid 2-pyridylmethyl ester



C25 H24 N4 O3; Mol wt: 428.4896

ACTION – Agent for the treatment of CNS disorders such as anxiety, sleep disorders, memory disorders and epilepsy that interacts with the modulatory sites on the GABA_A receptor complex (positive modulation) and has a favorable pharmacokinetic profile. Compound exhibited an IC₅₀ value of 0.002 μM against [³H]-flunitrazepam binding in rat cerebral cortex. It also inhibited pentylenetetrazol-induced clonic convulsions in mice at low doses. Within this series of 1-phenylbenzimidazole compounds, the following are also included:



Compound	R1	Formula
266145	i-Pr	C ₁₉ H ₂₆ FN ₅ O ₂
266146	Et	C ₁₈ H ₂₄ FN ₅ O ₂

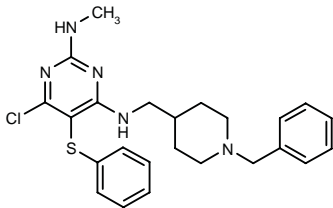
SOURCE – ADIR.

REFERENCES

1. Peglion, J.-L. et al. (ADIR et Cie.) 3-(Piperid-4-yl)-1,2-benzisoxazole and 3-(piperazin-4-yl)-1,2-benzisoxazole cpds. US 5780474.

266254

4-(1-Benzylpiperidin-4-ylmethylamino)-6-chloro-2-(methylamino)-5-(phenylsulfanyl)pyrimidine



C24 H28 Cl N5 S; Mol wt: 454.0392

ACTION – Agent for the treatment of neuropsychological disorders such as schizophrenia, mania, depression, Parkinson’s disease, substance abuse and Alzheimer’s disease, a dopamine D₄ receptor antagonist reported to possess negligible affinity for α₁-adrenoceptors.

SOURCE – Sumitomo.

REFERENCES

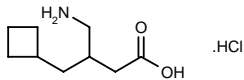
1. Igarashi, J. et al. (Sumitomo Pharmaceuticals Co., Ltd.) Pyrimidine derivs. useful for psychotropic agents. JP 98109937.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

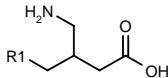
264870

3-(Aminomethyl)-4-cyclobutylbutyric acid hydrochloride



C9 H17 N O2 . HCl; Mol wt: 207.6992

ACTION – Agent for the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic disorders, pain, inflammation and gastrointestinal disorders, an analog of gabapentin with good binding affinity for the Ca²⁺ channel α2-δ subunit (IC₅₀ = 0.407 μM against [³H]-gabapentin binding to the α2-δ subunit derived from porcine brain tissue vs. 0.10-0.12 μM for gabapentin). Within this series of substituted γ-aminobutyric acids, the following are also specifically claimed:



Compound	R1	Formula
266117	cyclohexyl	C ₁₁ H ₂₁ NO ₂
266118	CH ₂ Ph	C ₁₂ H ₁₇ NO ₂
266119	CH ₂ SCH ₂ Ph	C ₁₃ H ₁₉ NO ₂ S
266120	4-Br-PhCH ₂ SCH ₂	C ₁₃ H ₁₈ BrNO ₂ S
266121	2,4-(Cl)2-PhCH ₂ SCH ₂	C ₁₃ H ₁₇ Cl ₂ NO ₂ S
266122	4-NH ₂ -PhCH ₂ OCH ₂	C ₁₃ H ₂₀ N ₂ O ₃
266123	4-CF ₃ -PhSCH ₂	C ₁₃ H ₁₆ F ₃ NO ₂ S
266124	4-Me-PhSCH ₂	C ₁₃ H ₁₉ NO ₂ S
266125	4-Cl-PhCH ₂ CH ₂ S	C ₁₃ H ₁₈ ClNO ₂ S
266126	3,4-(Cl)2-PhCH ₂ CH ₂ S	C ₁₃ H ₁₇ Cl ₂ NO ₂ S
266127	4-Me-PhCH ₂ S	C ₁₃ H ₁₉ NO ₂ S
266128	4-Br-PhS	C ₁₁ H ₁₄ BrNO ₂ S
266129	3,4-(Cl)2-PhCH ₂ S	C ₁₂ H ₁₅ Cl ₂ NO ₂ S
266130	cyclopropyl	C ₈ H ₁₆ ClNO ₂
266131	4-t-Bu-PhO	C ₁₅ H ₂₃ NO ₃

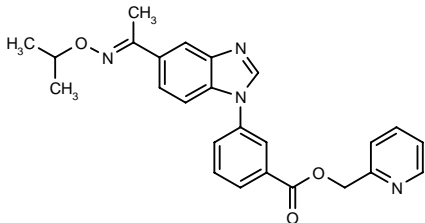
SOURCE – Warner-Lambert.

REFERENCES

1. Bryans, J.S. et al. (Warner-Lambert Co.) Substd. γ-aminobutyric acids as pharmaceutical agents. WO 9817627.

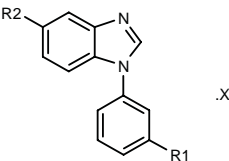
264879

3-[5-[1-(Isopropoxyimino)ethyl]benzimidazol-1-yl]benzoic acid 2-pyridylmethyl ester



C25 H24 N4 O3; Mol wt: 428.4896

ACTION – Agent for the treatment of CNS disorders such as anxiety, sleep disorders, memory disorders and epilepsy that interacts with the modulatory sites on the GABA_A receptor complex (positive modulation) and has a favorable pharmacokinetic profile. Compound exhibited an IC₅₀ value of 0.002 μM against [³H]-flunitrazepam binding in rat cerebral cortex. It also inhibited pentylenetetrazol-induced clonic convulsions in mice at low doses. Within this series of 1-phenylbenzimidazole compounds, the following are also included:



Compound	R1	R2	X	Formula
265754	1-Me-3-Pip	C(Me)=NOEt		C ₂₃ H ₂₆ N ₄ O
265755	1-pyrrolidiny	CN		C ₁₈ H ₁₆ N ₄
265756	1-Me-3-Pip	CH=NOH		C ₂₀ H ₂₂ N ₄ O
265757	4-(CH ₂ CH ₂ OH)-1-Piz	3-furyl		C ₂₃ H ₂₄ N ₄ O ₂
265758	4-(MeOCOCH ₂)-1-Piz	CO ₂ Et	HCl	C ₂₃ H ₂₆ N ₄ O ₄ .HCl
265759	1-Me-3-Pip	3-Pyr-CH ₂ OCO		C ₂₆ H ₂₈ N ₄ O ₂
265760	4-Me-1-Piz	CH ₂ CO ₂ Me	HCl	C ₂₁ H ₂₄ N ₄ O ₂ .HCl
265761	4-(CH ₂ CH ₂ OH)-1-Piz	C(Me)=NO-CH ₂ CO ₂ Me		C ₂₄ H ₂₄ N ₄ O ₄
265762	4-(EtOCOCH ₂)-1-Pip	C(Me)=NOEt		C ₂₆ H ₃₂ N ₄ O ₃
265763	CO ₂ Et	5-isoxazolyl		C ₁₉ H ₁₅ N ₃ O ₃
265764	2-Pyr-CH ₂ OCO	Ph		C ₂₆ H ₁₉ N ₃ O ₂
265765	4-[(EtOCO)2C=CH]-1-Piz	3-furyl		C ₂₉ H ₃₀ N ₄ O ₅

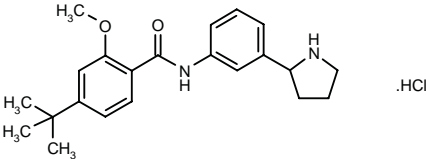
SOURCE – NeuroSearch.

REFERENCES

1. Teuber, L. and Wätjen, F. (NeuroSearch A/S) 1-Phenyl-benzimidazole cpds. and their use as GABA-A receptor modulators. WO 9817651.

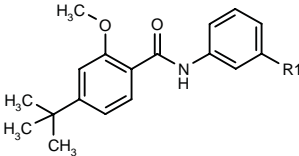
266212

4-*tert*-Butyl-2-methoxy-*N*-[3-(2-pyrrolidinyl)phenyl]-benzamide hydrochloride



C₂₂ H₂₈ N₂ O₂ . HCl; Mol wt: 388.9361

ACTION – Anticonvulsant also reported to be useful in the treatment or prevention of anxiety, depression, mania, drug and alcohol withdrawal symptoms, migraine, Alzheimer’s disease, Parkinson’s disease, sleep disorders and traumatic brain injury. Compound exhibits high affinity for the [³H]-SB-204269 binding site in rat forebrain membranes (pK_i > 7). Anticonvulsant activity was demonstrated in the maximal electroshock seizure (MES) threshold test in mice, where it gave a 53% increase in seizure threshold at 10 mg/kg p.o. Other specifically claimed compounds from this series of substituted benzamides include the following:



Compound	R1	Formula
267195	1-Me-2-Pip	C ₂₄ H ₃₂ N ₂ O ₂
267196	1-Me-2-pyrrolidinyl	C ₂₃ H ₃₀ N ₂ O ₂

SOURCE – SmithKline Beecham.

REFERENCES

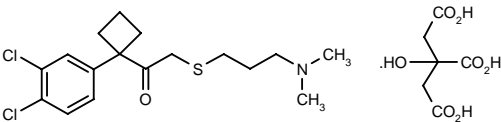
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

BTS-74398*

264071
217773 (as hydrochloride)

1-[1-(3,4-Dichlorophenyl)cyclobutyl]-2-[3-(dimethyl-amino)propylsulfanyl]ethanone monocitrate



C₁₇ H₂₃ Cl₂ N O S . C₆ H₈ O₇; Mol wt: 552.4689

ACTION – Potent monoamine reuptake inhibitor, as demonstrated *in vitro* (K_i = 4.2, 6.9 and 19 nM, respectively, for dopamine, norepinephrine and 5-HT), that does not induce the release of the monoamines. *In vivo* in rats, it potentiated apomorphine-induced climbing with an ED₆₀ of 29 mg/kg p.o., and it significantly reduced the concentrations of the norepinephrine metabolite MHPG (10 mg/kg p.o.) and the 5-HT precursor 5-HTP (30 mg/kg p.o.). The compound (5.0-20.0 mg/kg p.o.) produced a mild, dose-related and prolonged reversal of MPTP-induced motor deficits in common marmosets and reduced disability scores. It is suggested to have potential for treating not only the motor deficits associated with Parkinson’s disease, but also the depression that often accompanies the disorder.

SOURCE – Knoll.

REFERENCES

1. Harris, P.J. and Heal, D.J. (The Boots Company plc) 1-Arylcycloalkyl sulphides, sulphoxides and sulphones for the treatment of depression, anxiety and Parkinson’s disease. EP 715620, JP 96510222, US 5652271, WO 9426704.

2. Cheetham, S. et al. BTS 74 398: A novel monoamine reuptake inhibitor for the treatment of Parkinson’s disease. Br J Pharmacol 1998, 123(Suppl.): Abst 224P.

3. Jackson, H.C. et al. Behavioural effects of the monoamine reuptake inhibitor, BTS 74398, in rats and mice. Br J Pharmacol 1998, 123(Suppl.): Abst 256P.

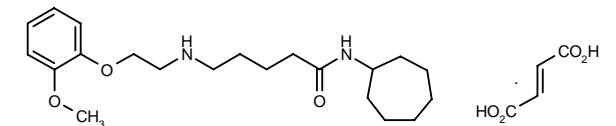
4. Smith, L.A. et al. BTS 74 398 reverses motor deficits in MPTP-treated common marmosets without inducing dyskinesias. Br J Pharmacol 1998, 123(Suppl.): Abst 253P.

*Identified compound 217773 Drug Data Report 1995, 017(04): 0325.

TREATMENT OF NAUSEA AND VOMITING

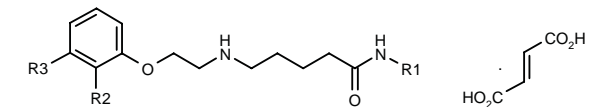
264380

N-Cycloheptyl-5-[2-(2-methoxyphenoxy)ethylamino]pentanamide fumarate



C21 H34 N2 O3 . C4 H4 O4; Mol wt: 478.5822

ACTION – Agent with high affinity for 5-HT_{1A} receptors (K_i = 0.098 nM), claimed for the treatment of emesis, gastrointestinal motility disorders, anxiety, depression, sleep disorders and cardiovascular disorders such as hypertension. A representative compound from a series of phenoxyethylamine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
266945	t-Bu	OMe	H	C ₁₈ H ₃₀ N ₂ O ₃ ·C ₄ H ₄ O ₄
266946	cyclohexyl	OMe	H	C ₂₀ H ₃₂ N ₂ O ₃ ·C ₄ H ₄ O ₄
266947	t-BuCH ₂	OMe	H	C ₁₉ H ₃₂ N ₂ O ₃ ·C ₄ H ₄ O ₄
266948	cyclopentyl	OMe	H	C ₁₉ H ₃₀ N ₂ O ₃ ·C ₄ H ₄ O ₄
266949	t-BuCH ₂	H	NHCONH ₂	C ₁₉ H ₃₂ N ₄ O ₃ ·C ₄ H ₄ O ₄
266950	cycloheptyl	H	NHCONH ₂	C ₂₁ H ₃₄ N ₄ O ₃ ·C ₄ H ₄ O ₄
266951	cycloheptyl	H	NHAc	C ₂₂ H ₃₅ N ₃ O ₃ ·C ₄ H ₄ O ₄
266952	t-BuCH ₂	H	NHAc	C ₂₀ H ₃₃ N ₃ O ₃ ·C ₄ H ₄ O ₄

SOURCE – SCRAS.

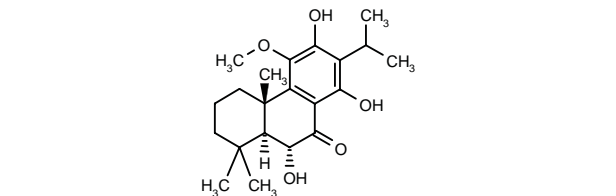
REFERENCES

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COGNITION-ENHANCING DRUGS

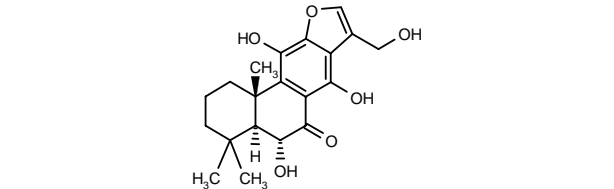
265097

[4a*S*-(4aα,10β,10aβ)]-6,8,10-Trihydroxy-7-isopropyl-5-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-9-one



C21 H30 O5; Mol wt: 362.4630

ACTION – Agent for the treatment of memory impairment, a diterpene isolated from *Lycopodium crassum* Willd. with glutamate transporter-inhibitory activity (IC₅₀ = 37 μM for inhibition of [³H]-glutamic acid uptake in rat neuronal cells). Another related compound is:



266027: C20 H24 O6

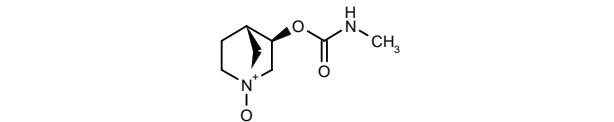
SOURCE – Shionogi.

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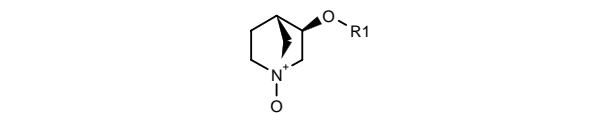
265540

exo-N-Methylcarbamic acid 1-oxido-1-azabicyclo[2.2.1]-hept-3-yl ester



C8 H14 N2 O3; Mol wt: 186.2096

ACTION – Agent for the treatment of cognition disorders with central muscarinic M₁ receptor-agonist activity. Other specifically claimed compounds from this series of 1-azabicycloheptane derivatives include the following:



Compound	R1	Isomer	Formula
265706	CONHMe	(-)	C ₈ H ₁₄ N ₂ O ₃
265707	CSNHMe		C ₈ H ₁₄ N ₂ O ₂ S
265708	CSNHMe	(+)	C ₈ H ₁₄ N ₂ O ₂ S
265709	CSNHMe	(-)	C ₈ H ₁₄ N ₂ O ₂ S
265710	CONHEt	(+)	C ₉ H ₁₆ N ₂ O ₃
265711	CONHEt	(-)	C ₉ H ₁₆ N ₂ O ₃
265712	CONHCH ₂ CF ₃		C ₉ H ₁₃ F ₃ N ₂ O ₃
265713	CONHCH ₂ CF ₃	(-)	C ₉ H ₁₃ F ₃ N ₂ O ₃
265714	CONHCH ₂ CF ₃	(+)	C ₉ H ₁₃ F ₃ N ₂ O ₃
265715	cyclopropyl-NHCO		C ₁₀ H ₁₆ N ₂ O ₃
265716	cyclopropyl-NHCO	(-)	C ₁₀ H ₁₆ N ₂ O ₃
265717	cyclopropyl-NHCO	(+)	C ₁₀ H ₁₆ N ₂ O ₃
265718	ethynyl-CH ₂ NHCO	(-)	C ₁₀ H ₁₄ N ₂ O ₃
265719	ethynyl-CH ₂ NHCO	(+)	C ₁₀ H ₁₄ N ₂ O ₃

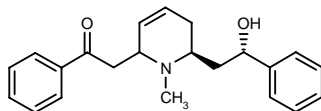
SOURCE – American Home Products.

REFERENCES

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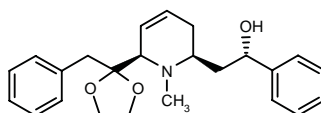
266213

2-[6(S)-[2(S)-Hydroxy-2-phenylethyl]-1-methylpiperidin-2-yl]-1-phenylethanone



C22 H25 N O2; Mol wt: 335.4445

ACTION – Agent for the treatment of memory impairment associated with aging, Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders with affinity for nicotinic receptors, particularly the $\alpha 7$ subtype. It is reported to protect against cognitive deficits induced in rats by cholinergic blockade. Another specifically claimed compound from this series of tetrahydropyridine derivatives is:



267219: C24 H29 N O3

SOURCE – ADIR.

REFERENCES

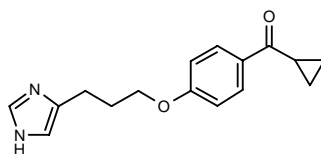
1. Marazano, C. et al. (ADIR et Cie.) *Novel subst. tetrahydropyridin derivs., method of preparation and pharmaceutical compns. containing them.* WO 9824765.

CIPROXIFAN*

242167

Cyclopropyl[4-[3-(1*H*-imidazol-4-yl)propoxy]phenyl]-methanone

FUB-359



C16 H18 N2 O2; Mol wt: 270.3302

ACTION – Potent, selective and competitive histamine H_3 receptor antagonist, as demonstrated by inhibition of [3H]-histamine release from rat synaptosomes ($K_i = 0.5 \pm 0.1$ nM) and in the [^{125}I]-iodoproxyfan binding assay ($K_i = 0.7 \pm 0.2$ nM), with about 3 orders of magnitude lower affinity for other receptors (histamine, muscarinic and 5-HT receptors and α - and β -adrenoceptors); it increased central *tele*-methylhistamine levels after oral administration in mice with an ED_{50} of 0.14 ± 0.03 mg/kg p.o., with a long duration of action and a bioavailability of 62%. Toxicological studies are currently in progress. Potentially useful in the treatment of dementia, Alzheimer's disease, epilepsy and schizophrenia.

SOURCES – Bioprojet; INSERM.

REFERENCES

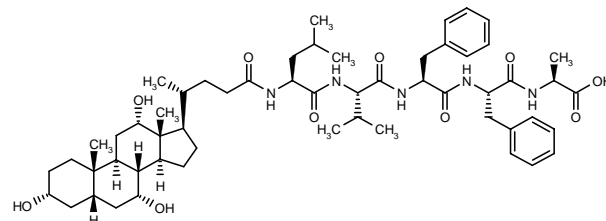
1. Schwartz, J.-C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *Imidazole derivs. as histamine receptor H_3 (ant)agonists.* EP 760811, FR 2732017, JP 98501001, WO 9629315.
2. Morisset, S. et al. *Effect of atypical neuroleptics on histaminergic neuron activity: Evidence for serotonin implication.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst W 11.8.
3. Stark, H. et al. *Ciproxifan, a selective antagonist of high in vitro and in vivo potency at histamine H_3 -receptors.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 9.9.
4. Stark, H. et al. *Optimization of 4-(3-(phenoxy)propyl)-1*H*-imidazoles leading to ciproxifan, a novel potent antagonist for the third histamine receptor subtype.* Eur J Pharm Sci 1998, 6(Suppl. 1): Abst 144.
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*Identified compound **242167** Drug Data Report 1997, 019(02): 0122.

PPI-368

264073

(3 α ,5 β ,7 α ,12 α)-Trihydroxycholan-24-oyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-alanine



C56 H83 N5 O10; Mol wt: 986.2967

ACTION – Low-molecular-weight peptido-organic compound that acts as a potent and selective inhibitor of amyloid β -peptide ($A\beta$) polymerization and blocks the formation of all neurotoxic species of $A\beta$ oligomers and fibril growth. Potentially useful as a lead for the development of therapeutic agents for the treatment of Alzheimer's disease.

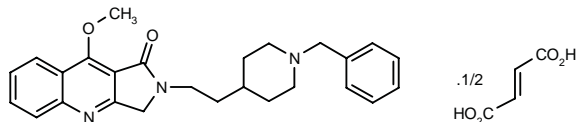
SOURCE – Praecis.

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1. Findeis, M.A. et al. (Praecis Pharmaceuticals Inc.) *Modulators of amyloid aggregation.* WO 9628471.
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3. Findeis, M.A. et al. *Discovery of PPI-368, a potent inhibitor of amyloid β -peptide polymerization.* Soc Neurosci Abstr 1996, 22(Part 3): Abst 764.7.
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5. Molineaux, S.M. et al. *Biochemical and biological characterization of PPI-368, a potent inhibitor of amyloid β -peptide polymerization.* Soc Neurosci Abstr 1996, 22(Part 3): Abst 651.1.

T-82***261618****184545** (as free base)

2-[2-(1-Benzylpiperidin-4-yl)ethyl]-9-methoxy-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate

C₂₆ H₂₉ N₃ O₂ . 1/2 C₄ H₄ O₄; Mol wt: 473.5697

ACTION – Acetylcholinesterase inhibitor proven to dose-dependently improve memory retention in scopolamine-treated rats by 50% at 0.03 mg/kg p.o., 92% at 0.1 mg/kg p.o. and 96% at 0.3 mg/kg p.o. The compound also appears to act as a 5-HT₃ receptor antagonist, which could lead to enhanced presynaptic acetylcholine release in cholinergic neurons. This dual activity profile may result in synergistic effects in the treatment of Alzheimer's disease. The compound has also shown a high therapeutic index following oral administration in mice.

SOURCES – Arena; SS Pharm.**REFERENCES**

1. Hasegawa, H. et al. (SS Pharmaceutical, Ltd.) *Quinoline derivs.* EP 481429, JP 93009188, JP 93279355, US 5190951, US 5240934, US 5300517.

2. Hayashi, H. et al. *Acetylcholinesterase inhibitory effect of T-82, a quinoline derivative, and its main metabolite, and evaluation for cerebral transmission thereof.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 31(YP) 12-7.

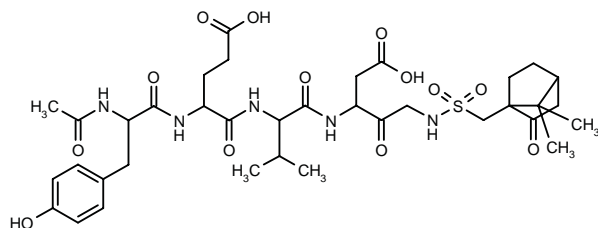
3. *SS Pharm. licenses AChE inhibitor to Arena.* Daily Essentials 1998, Feb 13.

MONOGRAPH – Mucke, H.A.M. and Castañer, J. *T-82.* Drugs Fut 1998, 23(10): in press.

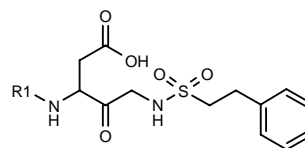
*Identified compound **184545** Drug Data Report 1992, 014(10): 0861.

**TREATMENT OF
CEREBROVASCULAR DISEASES****264836**

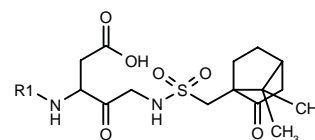
3-(Acetyl-DL-tyrosyl-DL-glutamyl-DL-valylamino)-5-(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethylsulfonamido)-4-oxopentanoic acid

C₃₆ H₅₁ N₅ O₁₃ S; Mol wt: 793.8869

ACTION – Agent for the treatment of stroke, reperfusion injury, Alzheimer's disease, inflammatory disorders and septic shock, an inhibitor of IL-1 β -converting enzyme (ICE or caspase-1; K_i = 0.11 nM; IC₅₀ = 0.002 μ M) and of other cysteine proteases from the ICE family such as Ich-2 (caspase-4; IC₅₀ = 0.7 μ M). Other compounds from this series of sulfonamide derivatives include the following:



Compound	R1	Formula
265728	PhCH ₂ OCO-DL-Val-DL-Ala-	C ₂₉ H ₃₈ N ₄ O ₉ S
265729	PhCH ₂ OCO-DL-Glu-DL-Val-	C ₃₁ H ₄₀ N ₄ O ₁₁ S
265730	PhCH ₂ CH ₂ CO-DL-Glu-DL-Val-	C ₃₂ H ₄₂ N ₄ O ₁₀ S
265731	Ac-DL-Tyr-DL-Glu-DL-Val-	C ₃₄ H ₄₅ N ₅ O ₁₂ S



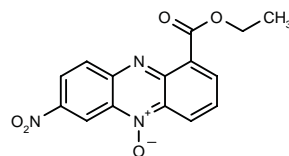
Compound	R1	Isomer	Formula
265732	Ac-DL-Val	S	C ₂₂ H ₃₅ N ₃ O ₉ S
265733	PhCH ₂ OCO-DL-Val-DL-Ala-		C ₃₁ H ₄₄ N ₄ O ₁₀ S
265734	PhCH ₂ CH ₂ CO-DL-Glu-DL-Val-		C ₃₄ H ₄₈ N ₄ O ₁₁ S
265735	PhCH ₂ OCO-DL-Glu-DL-Val-		C ₃₃ H ₄₆ N ₄ O ₁₂ S

SOURCE – Warner-Lambert.**REFERENCES**

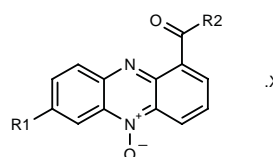
1. Albrecht, H.P. et al. (Warner-Lambert Co.) *Sulfonamide interleukin-1 β converting enzyme inhibitors.* WO 9816505.

264840

7-Nitro-5-oxidophenazine-1-carboxylic acid ethyl ester

C₁₅ H₁₁ N₃ O₅; Mol wt: 313.2679

ACTION – Agent for the treatment of neurodegenerative disorders that acts by inhibiting neuronal cell death. Compound exhibited EC₅₀ values of 1.9 and 1.8 nM, respectively, against glutamic acid- and BSO-induced toxicity in N18-RE-105 cells, and an EC₂₅ value of 1.5 nM against glutamic acid-induced toxicity in rat fetal hippocampal cells. Compound also exhibited lipid peroxidation-inhibitory activity (59.2% inhibition at 100 μ M in rat brain homogenates). Within this series of phenazine 5-oxide derivatives, the following are also included:



Compound	R1	R2	X	Formula
265988	COPh	OEt		C ₂₂ H ₁₈ N ₂ O ₄
265989	NO ₂	O(CH ₂) ₃ N(Me) ₂	HCl	C ₁₈ H ₁₈ N ₄ O ₅ .HCl
265990	NO ₂	NH(CH ₂) ₃ N(Me) ₂	HCl	C ₁₈ H ₁₉ N ₅ O ₄ .HCl

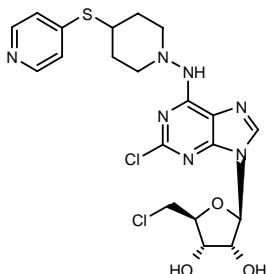
SOURCE – Nippon Chemiphar.

REFERENCES

1. Takahashi, T. et al. (Nippon Chemiphar Co., Ltd.) *Phenazine 5-oxide derivs.* WO 9816516.

264852

2,5'-Dichloro-5'-deoxy-*N*⁶-[4-(4-pyridylsulfanyl)piperidin-1-yl]adenosine



C20 H23 Cl2 N7 O3 S; Mol wt: 512.4197

ACTION – Agent for the treatment of cerebral and myocardial ischemia, as well as epilepsy, with high and selective affinity for adenosine A₁ receptors ($K_i = 14$ nM) relative to A₂ receptors ($K_i = 10,700$ nM) and which is reported to have relatively high lipophilicity, making it suitable for passage across the blood–brain barrier. It is reported to be more potent than other adenosine agonists in a gerbil model of severe temporary forebrain ischemia.

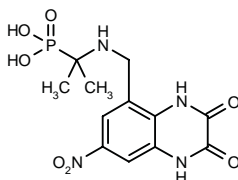
SOURCE – Novo Nordisk.

REFERENCES

1. Knutsen, L. (Novo Nordisk A/S) *Novel therapeutically active adenosine derivs.* WO 9816539.

264890

1-Methyl-1-(7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquin-oxalin-5-ylmethylamino)ethylphosphonic acid



C12 H15 N4 O7 P; Mol wt: 358.2455

ACTION – Neuroprotective agent, an excitatory amino acid receptor antagonist. A representative compound from a series of substituted aminoalkane phosphonic acids.

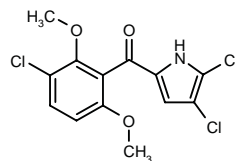
SOURCE – Novartis.

REFERENCES

1. Acklin, P. et al. (Novartis AG) *Substd. aminoalkane phosphonic acids.* WO 9817672.

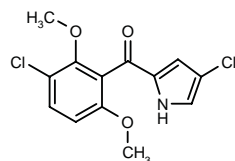
265099

1-(3-Chloro-2,6-dimethoxyphenyl)-1-(4,5-dichloropyrrol-2-yl)methanone



C13 H10 Cl3 N O3; Mol wt: 334.5850

ACTION – Neuroprotective and cerebral antiischemic agent that acts by blocking the release of glutamate. *In vivo*, compound significantly inhibited cerebral edema produced by ligation of the middle cerebral artery in rats following intracerebral administration. Another compound from this series of aromatic ketones is:



266028: C13 H11 Cl2 N O3

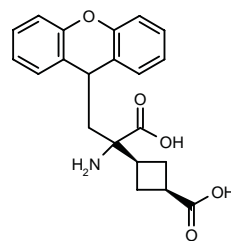
SOURCE – Shionogi.

REFERENCES

1. Oshima, T. et al. (Shionogi & Co. Ltd.) *Glutamate release inhibitor and novel cpds.* WO 9818760.

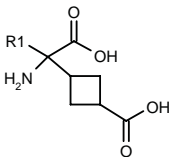
265142

cis-2-Amino-2-(3-carboxycyclobutyl)-3-(9-xanthyl)-propionic acid

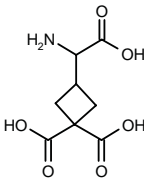


C21 H21 N O5; Mol wt: 367.3989

ACTION – Neuronal injury inhibitor that acts by interacting with metabotropic glutamate receptors, also reported to possess antipsychotic, anticonvulsant, analgesic and antiemetic activity. A compound within a series of cyclobutyl derivatives, wherein the following are also included:



Compound	R1	Isomer	Formula
267111	xanthen-9-yl-CH2	trans	C ₂₁ H ₂₁ NO ₅
267112	H	cis	C ₇ H ₁₁ NO ₄
267114	thioxanthen-9-yl-CH2	cis	C ₂₁ H ₂₁ NO ₄ S
267115	thioxanthen-9-yl-CH2	trans	C ₂₁ H ₂₁ NO ₄ S
267116	9-OH-10-oxo-thioxanthen-9-yl-CH2	cis	C ₂₁ H ₂₁ NO ₆ S
267117	9-OH-10-oxo-thioxanthen-9-yl-CH2	trans	C ₂₁ H ₂₁ NO ₆ S
267118	10,10-dioxo-thioxanthen-9-yl-CH2	cis	C ₂₁ H ₂₁ NO ₆ S



267113: C8 H11 N O6

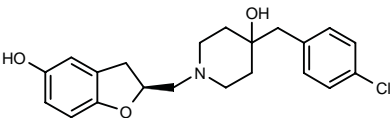
SOURCE – Lilly.

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1. Clark, B.P. and Harris, J.R. (Eli Lilly and Company) *Pharmaceutical acidic cpds.* EP 837061, JP 98120635.

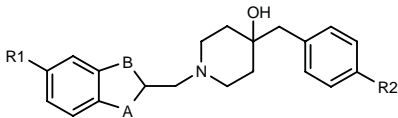
265426

4-(4-Chlorobenzyl)-1-[5-hydroxy-2,3-dihydrobenzofuran-2(S)-ylmethyl]piperidin-4-ol



C21 H24 Cl N O3; Mol wt: 373.8776

ACTION – Neuroprotective agent for the treatment of conditions such as stroke, brain trauma, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and neurodegeneration associated with bacterial and viral infections, a selective antagonist of NMDA receptor subtypes, particularly the NR2B subtype as compared to the NR2A subtype, as demonstrated in a voltage clamp experiment in oocytes expressing recombinant NMDA receptors (90% inhibition at 0.1 μM for the NR2B subtype vs. 9% inhibition at 10 μM for the NR2A subtype). In binding assays, compound exhibited IC₅₀ values of 0.005 and 6.0 μM against [³H]-Ro-25-6981 and [³H]-prazosin binding, respectively. Other specifically claimed compounds from this series of 4-hydroxypiperidines include the following:



Compound	R1	R2	A	B	Isomer	Formula
267129	OH	Me	-O-	-CH2-		C ₂₂ H ₂₇ NO ₃
267130	OH	H	-O-	-CH2-		C ₂₁ H ₂₅ NO ₃
267131	OH	F	-O-	-CH2-		C ₂₁ H ₂₄ FNO ₃
267132	OH	Et	-O-	-CH2-		C ₂₃ H ₂₉ NO ₃
267133	OH	Me	-O-	-CH2-	S	C ₂₂ H ₂₇ NO ₃
267134	NHSO2Me	Me	-O-	-CH2-		C ₂₃ H ₃₀ N ₂ O ₄ S
267135	OH	Me	-CH(OH)-	-CH2-	cis	C ₂₃ H ₂₉ NO ₃
267136	OH	Me	-CH(OH)-	-CH2-	trans	C ₂₃ H ₂₉ NO ₃
267137	OH	Me	-CH(OH)-	-(CH2)2-	trans	C ₂₄ H ₃₁ NO ₃
267138	OH	H	-CH(OH)-	-(CH2)2-	trans	C ₂₃ H ₂₉ NO ₃
267139	OH	Me	-CH2-	-CH2-		C ₂₃ H ₂₉ NO ₂
267140	OH	H	-CH2-	-(CH2)2-		C ₂₃ H ₂₉ NO ₂
267141	OH	Me	-NH-	-CH2-		C ₂₂ H ₂₈ N ₂ O ₂

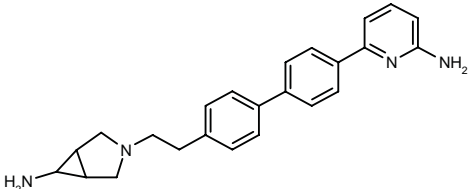
SOURCE – Roche.

REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *4-Hydroxy-piperidine derivs.* EP 846683, JP 98168060.

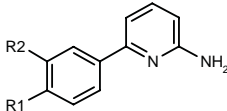
266214

3-[2-[4'-(6-Aminopyridin-2-yl)biphenyl-4-yl]ethyl]-3-azabicyclo[3.1.0]hexan-6-ylamine

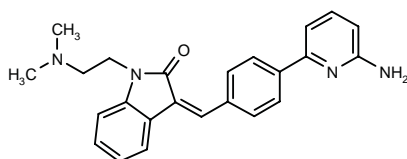


C24 H26 N4; Mol wt: 370.4974

ACTION – Agent for the treatment and prevention of CNS disorders, inflammatory disorders and septic shock, an inhibitor of the inducible and neuronal isoforms of nitric oxide synthase (NOS). A representative compound from a series of 6-phenylpyridyl-2-amine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
267197	3-[NH2CH(Me)CONH]-Ph	H	C ₂₀ H ₂₀ N ₄ O
267198	1-[CH(Ph)2CH2]- -2-Pip-CH2	H	C ₃₁ H ₃₃ N ₃
267199	H	2-(cyclohexyl-NH)- -cyclopentyl-CH2	C ₂₃ H ₃₁ N ₃
267200	2-(EtOCH2CH2NH)- -cyclohexyl-CH2	H	C ₂₂ H ₃₁ N ₃ O
267203	1-[3,4-(MeO)2-PhCH2]- -4-Pip	H	C ₂₅ H ₂₉ N ₃ O ₂
267204	1-(5-thiazolyl-CH2)-4-Pip	H	C ₂₀ H ₂₂ N ₄ S
267205	1-(4-Pyr-CH2)-4-Pip	H	C ₂₂ H ₂₄ N ₄
267206	3-(PhCH2)-8-OH-3-aza- bicyclo[3.2.1]octan-8-yl	H	C ₂₅ H ₂₇ N ₃ O



267202: C₂₄ H₂₄ N₄ O

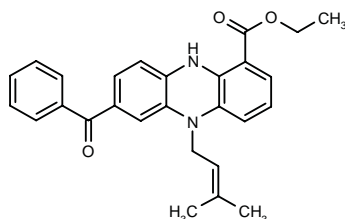
SOURCE – Pfizer.

REFERENCES

1. Lowe, J.A. III (Pfizer Inc.) 6-Phenylpyridyl-2-amine derivs. useful as NOS inhibitors. WO 9824766.

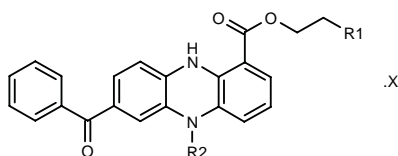
266217

7-Benzoyl-5-(3-methyl-2-butenyl)-5,10-dihydrophenazine-1-carboxylic acid ethyl ester



C₂₇ H₂₆ N₂ O₃; Mol wt: 426.5134

ACTION – Agent for the treatment of cerebrovascular disorders that acts by inhibiting glutamate neurotoxicity and lipid peroxidation. Compound exhibited EC₅₀ values of 14.5 and 96.2 nM, respectively, against glutamic acid- and BSO-induced toxicity in N18-RE-105 cells, and an EC₂₅ value of 12 nM against glutamic acid-induced toxicity in rat fetal hippocampal cells. Compound also exhibited lipid peroxidation-inhibitory activity, producing 60.2% inhibition at 100 µM in rat brain homogenates. Within this series of dihydrophenazinecarboxylic acid derivatives, the following are also included:



Compound	R1	R2	X	Formula
267247	H	H		C ₂₂ H ₁₈ N ₂ O ₃
267248	H	CH ₂ Ph		C ₂₃ H ₂₄ N ₂ O ₃
267249	H	Me		C ₂₃ H ₂₀ N ₂ O ₃
267250	CH ₂ N(Me) ₂	CH ₂ CH=C(Me) ₂	HCl	C ₃₀ H ₃₃ N ₃ O ₃ ·HCl

SOURCE – Nippon Chemiphar.

REFERENCES

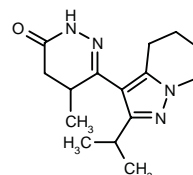
1. Takahashi, T. et al. (Nippon Chemiphar Co., Ltd.) Dihydrophenazinecarboxylic acid derivs. JP 98218864, WO 9824772.

RESPIRATORY DRUGS

ASTHMA THERAPY

264367

6-(2-Isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one



C₁₅ H₂₂ N₄ O; Mol wt: 274.3658

ACTION – Bronchodilating agent with inhibitory activity against phosphodiesterase (PDE) from the respiratory tract, especially phosphodiesterase type 5 (PDE5). A representative compound from a series of tetrahydropyrazolopyridine-pyridazinone derivatives.

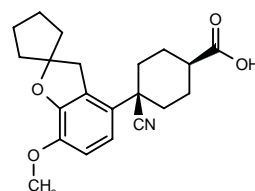
SOURCE – Kyorin.

REFERENCES

1. Kohno, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) Tetrahydropyrazolopyridine-pyridazinone derivs. and their preparation method. JP 98109988.

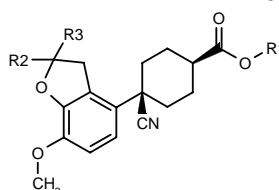
265519

cis-4-Cyano-4-(7-methoxyspiro[benzofuran-2(3H),1'-cyclopentan]-4-yl)cyclohexane-1-carboxylic acid



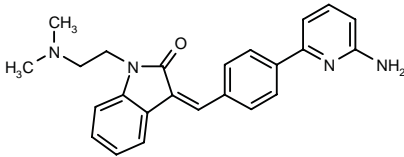
C₂₁ H₂₅ N O₄; Mol wt: 355.4315

ACTION – Antiasthmatic agent, an inhibitor of phosphodiesterase type 4 (PDE4; -log IC₅₀ = 8.31). Other specifically claimed compounds from this series of substituted dihydrobenzofurans include the following:



Compound	R1	R2,R3	Formula
266471	Me	-(CH ₂) ₄ -	C ₂₂ H ₂₇ NO ₄
266472	H	-CH ₂ CH ₂ OCH ₂ CH ₂ -	C ₂₁ H ₂₅ NO ₅

SOURCE – Byk Gulden.



267202: C24 H24 N4 O

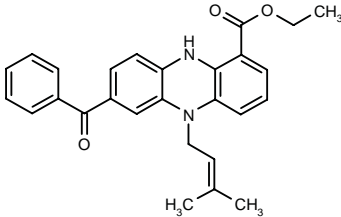
SOURCE – Pfizer.

REFERENCES

1. Lowe, J.A. III (Pfizer Inc.) *6-Phenylpyridin-2-amine derivs. useful as NOS inhibitors.* WO 9824766.

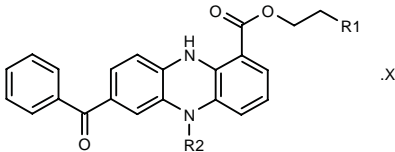
266217

7-Benzoyl-5-(3-methyl-2-butenyl)-5,10-dihydrophenazine-1-carboxylic acid ethyl ester



C27 H26 N2 O3; Mol wt: 426.5134

ACTION – Agent for the treatment of cerebrovascular disorders that acts by inhibiting glutamate neurotoxicity and lipid peroxidation. Compound exhibited EC₅₀ values of 14.5 and 96.2 nM, respectively, against glutamic acid- and BSO-induced toxicity in N18-RE-105 cells, and an EC₂₅ value of 12 nM against glutamic acid-induced toxicity in rat fetal hippocampal cells. Compound also exhibited lipid peroxidation-inhibitory activity, producing 60.2% inhibition at 100 µM in rat brain homogenates. Within this series of dihydrophenazinecarboxylic acid derivatives, the following are also included:



Compound	R1	R2	X	Formula
267247	H	H		C ₂₂ H ₁₈ N ₂ O ₃
267248	H	CH ₂ Ph		C ₂₃ H ₂₄ N ₂ O ₃
267249	H	Me		C ₂₃ H ₂₀ N ₂ O ₃
267250	CH ₂ N(Me) ₂	CH ₂ CH=C(Me) ₂	HCl	C ₃₀ H ₃₃ N ₃ O ₃ ·HCl

SOURCE – Nippon Chemiphar.

REFERENCES

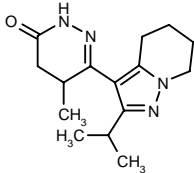
1. Takahashi, T. et al. (Nippon Chemiphar Co., Ltd.) *Dihydrophenazinecarboxylic acid derivs.* JP 98218864, WO 9824772.

RESPIRATORY DRUGS

ASTHMA THERAPY

264367

6-(2-Isopropyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one



C15 H22 N4 O; Mol wt: 274.3658

ACTION – Bronchodilating agent with inhibitory activity against phosphodiesterase (PDE) from the respiratory tract, especially phosphodiesterase type 5 (PDE5). A representative compound from a series of tetrahydropyrazolopyridine-pyridazinone derivatives.

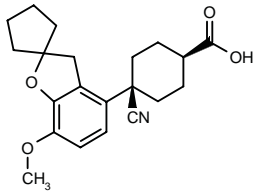
SOURCE – Kyorin.

REFERENCES

1. Kohno, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *Tetrahydropyrazolopyridine-pyridazinone derivs. and their preparation method.* JP 98109988.

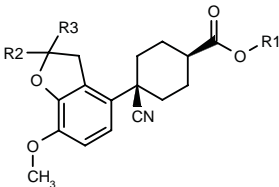
265519

cis-4-Cyano-4-(7-methoxyspiro[benzofuran-2(3H),1'-cyclopentan]-4-yl)cyclohexane-1-carboxylic acid



C21 H25 N O4; Mol wt: 355.4315

ACTION – Antiasthmatic agent, an inhibitor of phosphodiesterase type 4 (PDE4; -log IC₅₀ = 8.31). Other specifically claimed compounds from this series of substituted dihydrobenzofurans include the following:



Compound	R1	R2,R3	Formula
266471	Me	-(CH ₂) ₄ -	C ₂₂ H ₂₇ NO ₄
266472	H	-CH ₂ CH ₂ OCH ₂ CH ₂ -	C ₂₁ H ₂₅ NO ₅

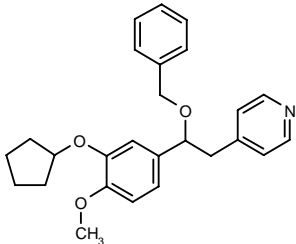
SOURCE – Byk Gulden.

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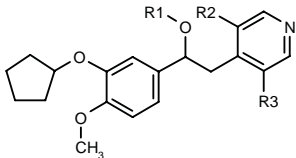
266086

4-[2-Benzoyloxy-2-(3-cyclopentyloxy-4-methoxyphenyl)-ethyl]pyridine



C26 H29 N O3; Mol wt: 403.5191

ACTION – Antiasthmatic and antiinflammatory agent, a selective inhibitor of phosphodiesterase type 4 (PDE4) with little or no activity against other PDE isozymes. Within this series of trisubstituted phenyl derivatives, the following are also specifically claimed:



Compound	R1	R2=R3	Formula
266142	Bu	H	C ₂₃ H ₃₁ NO ₃
266143	cyclohexyl-CH2	H	C ₂₆ H ₃₆ NO ₃
266144	Bu	Cl	C ₂₃ H ₂₉ Cl ₂ NO ₃
266163	CH2CH2OMe	Cl	C ₂₂ H ₂₇ Cl ₂ NO ₄

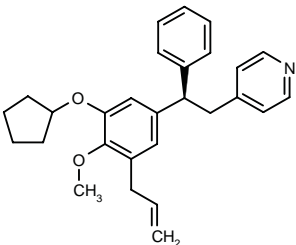
SOURCE – Celltech.

REFERENCES

1. Head, J.C. et al. (Celltech Group plc) *Trisubst. phenyl derivs. and processes for their preparation*. US 5780477.

266087

4-[2(R)-[3-Cyclopentyloxy-4-methoxy-5-(2-propenyl)-phenyl]-2-phenylethyl]pyridine



C28 H31 N O2; Mol wt: 413.5579

ACTION – Antiasthmatic and antiinflammatory agent, a selective inhibitor of phosphodiesterase type 4 (PDE4) with little or no activity against other PDE isozymes. A specifically claimed compound within a series of tetrasubstituted phenyl derivatives.

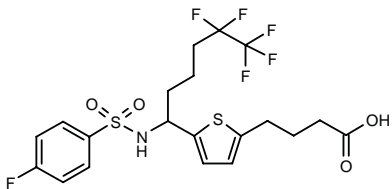
SOURCE – Celltech.

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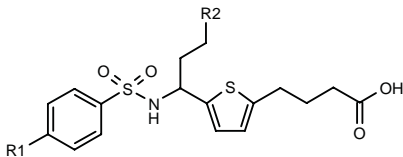
265481

4-[5-[5,5,6,6,6-Pentafluoro-1-(4-fluorophenyl)sulfon-amido)hexyl]-2-thienyl]butyric acid

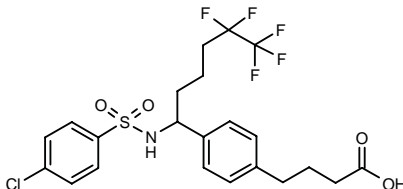


C20 H21 F6 N O4 S2; Mol wt: 517.5089

ACTION – Antithrombotic, antiasthmatic and antiallergic agent, a thromboxane A₂ and leukotriene D₄ (CysLT₁) receptor antagonist. *In vitro*, it inhibited U-46619- and LTD₄-induced guinea pig trachea contractions with pK_B values of 9.1 and 6.4, respectively. When administered to guinea pigs, it produced 92% inhibition of U-46619-induced bronchoconstriction at 0.3 mg/kg p.o., and exhibited an ED₅₀ value of 0.78 mg/kg p.o. for inhibition of LTD₄-induced bronchoconstriction. Compound was found to possess good stability to hepatic metabolism in an *in vitro* assay. A representative compound from a series of benzenesulfonamides, wherein the following are also included:



Compound	R1	R2	Formula
265991	Cl	CH2CF2CF3	C ₂₀ H ₂₁ ClF ₅ NO ₄ S ₂
265992	F	(CH2)3CF3	C ₂₁ H ₂₅ F ₄ NO ₄ S ₂
265993	F	(CF2)3CF3	C ₂₁ H ₁₉ F ₁₀ NO ₄ S ₂
265994	F	CH2CF2CF2CF3	C ₂₁ H ₂₁ F ₈ NO ₄ S ₂
265995	F	CH2CF(CF3)2	C ₂₁ H ₂₁ F ₈ NO ₄ S ₂
265996	F	CF2CF2CF3	C ₂₀ H ₁₉ F ₈ NO ₄ S ₂
265997	Cl	CH2CF2CF2CF3	C ₂₁ H ₂₁ ClF ₇ NO ₄ S ₂



265998: C22 H23 Cl F5 N O4 S

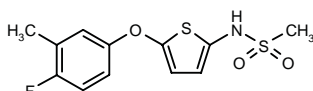
SOURCE – Hokuriku.

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1. Yasuda, S. et al. (Hokuriku Seiyaku Co., Ltd.) *Benzenesulfonamide derivs. and drugs containing the same*. JP 98195038, WO 9821177.

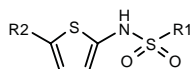
267273

N-[5-(4-Fluoro-3-methylphenoxy)thien-2-yl]methanesulfonamide



C12 H12 F N O3 S2; Mol wt: 301.3608

ACTION – A dual inhibitor of 5-lipoxygenase (5-LO) and cyclooxygenase type 2 (COX-2) with potential in the treatment of inflammation, asthma, arthritis, hypersensitivity, myocardial ischemia, skin disorders such as psoriasis and dermatitis, and gastrointestinal disorders such as inflammatory bowel disease. *In vitro*, compound inhibited 5-LO with IC₅₀ values of 0.02 and 0.31 μM in RBL-1 cell homogenates and whole RBL-1 cells, respectively, and it inhibited COX-2 in human umbilical cord endothelial ECV-304 cells with an IC₅₀ of 1.18 μM. A representative compound from a series of specifically claimed 2,5-disubstituted thiophenes, wherein the following are also included:



Compound	R1	R2	Formula
267274	Me	OPh	C ₁₁ H ₁₁ NO ₃ S ₂
267275	Me	3-Me-PhO	C ₁₂ H ₁₃ NO ₃ S ₂
267276	Me	3-CF ₃ -PhO	C ₁₂ H ₁₀ F ₃ NO ₃ S ₂
267277	Me	2,4-(Cl)2-PhO	C ₁₁ H ₉ Cl ₂ NO ₃ S ₂
267278	Ph	OPh	C ₁₆ H ₁₃ NO ₃ S ₂
267279	Me	4-F-2-Me-PhO	C ₁₂ H ₁₂ FNO ₃ S ₂
267280	Me	2,4-(F)2-PhO	C ₁₁ H ₉ F ₂ NO ₃ S ₂
267281	Me	1-Naph-O	C ₁₅ H ₁₃ NO ₃ S ₂
267282	Me	SC5H11	C ₁₀ H ₁₇ NO ₂ S ₃
267283	i-Pr	OPh	C ₁₃ H ₁₅ NO ₃ S ₂

SOURCE – Ortho-McNeil.

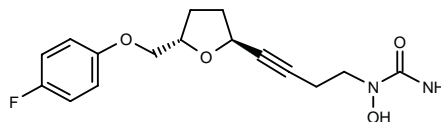
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CMI-977

230379

(2S,5S)-1-[4-[5-(4-Fluorophenoxymethyl)tetrahydrofuran-2-yl]-3-butynyl]-1-hydroxyurea



C16 H19 F N2 O4; Mol wt: 322.3341

ACTION – Potent, orally active 5-lipoxygenase (5-LO) inhibitor proven to inhibit 5-LO activity in human whole blood with an IC₅₀ of 120 nM and to block anti-IgE-induced contractions of human airways tissue with an IC₅₀ of 100 nM, being 5-10 times more potent than zileuton. The compound inhibited antigen-induced bronchoconstriction in guinea pigs with an ED₅₀ of 3 mg/kg p.o. (> 50% protection for over 6 h at 10 mg/kg p.o.), it prevented antigen-induced airways hyperresponsiveness in mice at 10 mg/kg p.o. b.i.d., it inhibited eosinophil influx into bronchoalveolar lavage (BAL) fluid in ovalbumin-challenged Brown Norway rats by 63% at a dose of 10 mg/kg p.o. b.i.d., and it effectively blocked both the early and late phases of the asthmatic response in a sheep model at 30 mg/kg p.o. b.i.d. It has high oral bioavailability (90% in monkeys) and a pharmacodynamic profile indicating the feasibility of twice-daily dosing, and it is currently undergoing phase I trials for the treatment of asthma.

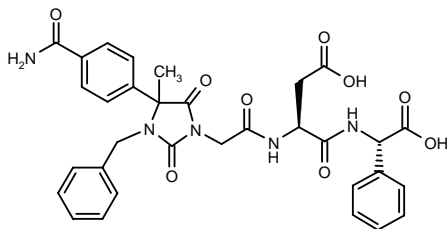
SOURCE – UCB.

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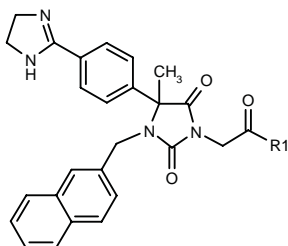
264672

N-[2-[3-Benzyl-4-(4-carbamoylphenyl)-4-methyl-2,5-dioximidazolidin-1-yl]acetyl]-L-aspartyl-L-phenylglycine



C32 H31 N5 O9; Mol wt: 629.6229

ACTION – Agent for the treatment or prevention of disorders involving leukocyte adhesion and migration and/or disorders involving adhesion processes mediated by the VLA-4 receptor such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the CNS, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, cancer and malaria. Compound was found to inhibit the adhesion of U937 cells to hVCAM-1(1-3)-Ig with an IC₅₀ value of 7.5 µM. Other heterocyclic compounds include the following:



Compound	R1	Formula
266514	-L-Asp-L-(2-Ph)Gly-OH	C ₃₈ H ₃₆ N ₆ O ₈
266515	(S)-1-adamantyl-CH2-OCONHCH(CO2H)CH2NH	C ₄₁ H ₄₆ N ₆ O ₇

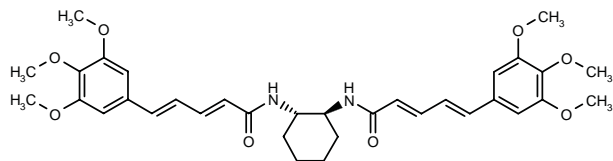
SOURCE – Hoechst Marion Roussel.

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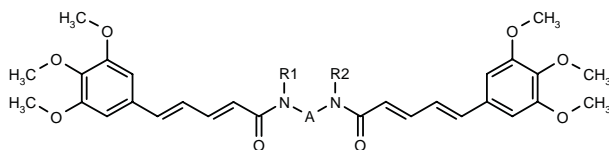
264835

trans-N,N'-Cyclohexane-1,2-diylbis[5-(3,4,5-trimethoxyphenyl)-2(*E*),4(*E*)-pentadienamides]

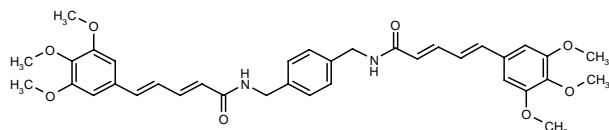


C34 H42 N2 O8; Mol wt: 606.7118

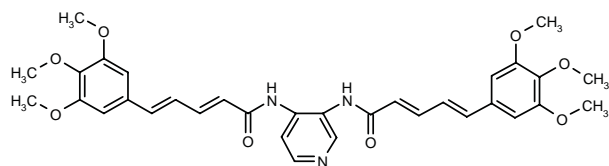
ACTION – Antiallergic agent proven to inhibit IgE antibody production in spleen cells of sensitized mice stimulated with lipopolysaccharide (LPS) and IL-4 (100% inhibition at 10 µM). Within this series of diamide derivatives, the following are also included:



Compound	R1=R2	A	Formula
265984	Me	-(CH2)6-	C ₃₆ H ₄₈ N ₂ O ₈
265986	H	1,2-Ph	C ₃₄ H ₃₆ N ₂ O ₈



265985: C36 H40 N2 O8



265987: C33 H35 N3 O8

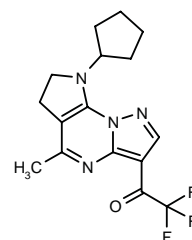
SOURCE – Kowa.

REFERENCES

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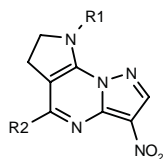
265266

1-(8-Cyclopentyl-5-methyl-7,8-dihydro-6*H*-pyrrolo[3,2-*e*]-pyrazolo[1,5-*a*]pyrimidin-3-yl)-2,2,2-trifluoroethanone



C16 H17 F3 N4 O; Mol wt: 338.3313

ACTION – Agent for the treatment of respiratory disorders proven to inhibit carbachol-, histamine-, LTD₄- and CTA₂-induced contractions of isolated guinea pig trachea preparations with pIC₅₀ values of 5.15, 5.75, 5.55 and 5.81, respectively. *In vivo*, compound inhibited acetylcholine- and histamine-induced bronchoconstriction in guinea pigs following i.v. (83.1 and 67.3% inhibition, respectively, at 1 mg/kg) and p.o. administration (53.7 and 38.9% inhibition, respectively, at 100 mg/kg), with little effect on blood pressure. A representative compound from a series of pyrrolo[3,2-*e*]pyrazolo[1,5-*a*]pyrimidines, wherein the following are also included:



Compound	R1	R2	Formula
266152	cyclopentyl	Me	C ₁₄ H ₁₇ N ₅ O ₂
266153	CH(Me)Et	Me	C ₁₃ H ₁₇ N ₅ O ₂
266154	cyclopentyl	NH2	C ₁₃ H ₁₆ N ₆ O ₂

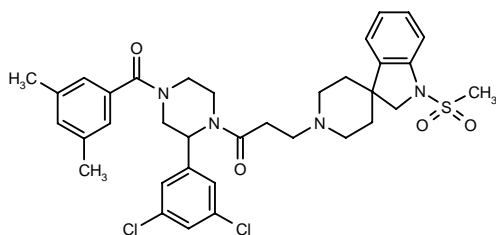
SOURCE – Pola Chemical.

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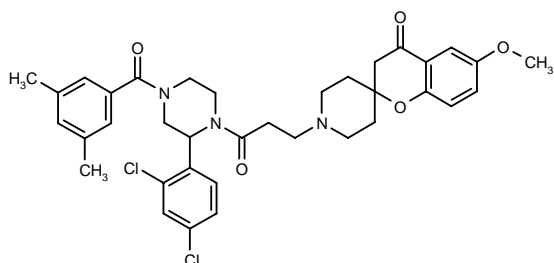
267220

2-(3,5-Dichlorophenyl)-4-(3,5-dimethylbenzoyl)-1-[3-[1-(methylsulfonyl)spiro[indole-3(2*H*),4'-piperidin]-1'-yl]-propionyl]piperazine



C₃₅ H₄₀ Cl₂ N₄ O₄ S; Mol wt: 683.6970

ACTION – Agent for the treatment of chronic airways disorders such as asthma, inflammatory, CNS and gastrointestinal disorders, autoimmune diseases and pain that acts by virtue of its neurokinin receptor-antagonist activity. Another compound from this series of substituted piperazine derivatives is:



267221: C₃₆ H₃₉ Cl₂ N₃ O₅

SOURCE – Schering-Plough.

REFERENCES

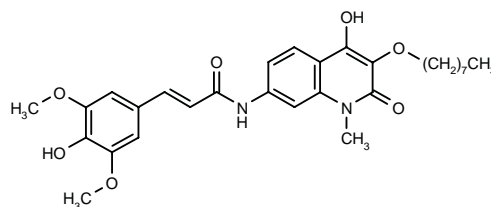
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TA-270*

256465

4-Hydroxy-*N*-(4-hydroxy-1-methyl-3-octyloxy-2-oxo-1,2-dihydroquinolin-7-yl)-3,5-dimethoxycinnamic acid amide

4-Hydroxy-7-(4-hydroxy-3,5-dimethoxycinnamoylamino)-1-methyl-3-octyloxy-2(1*H*)-quinolinone



C₂₉ H₃₆ N₂ O₇; Mol wt: 524.6104

ACTION – Antiallergic, antiinflammatory and antiasthmatic agent whose activity has been demonstrated in a murine model of contact dermatitis and another model of delayed-type hypersensitivity (DTH) reaction, the tuberculin-induced skin reaction in guinea pigs, as well as in guinea pig models of immediate (IAR) and late asthmatic responses (LAR). It is as effective as prednisolone in suppressing IAR and LAR and inflammatory cell infiltration of bronchoalveolar lavage fluid (BALF), and it was able to enhance the effects of prednisolone in the dual asthmatic response (DAR) in guinea pigs, suggesting particular efficacy in the treatment of chronic asthma attacks.

SOURCE – Dainippon Ink & Chemicals.

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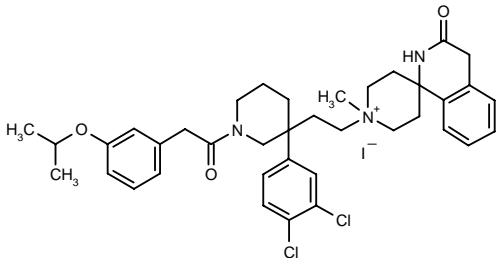
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*Identified compound **256465** Drug Data Report 1998, 020(02): 0125.

YM-49244*

234735

1'-[2-[3-(3,4-Dichlorophenyl)-1-[2-[3-(isopropoxy)-phenyl]acetyl]piperidin-3-yl]ethyl]-1'-methyl-3-oxospiro-[1,2,3,4-tetrahydroisoquinoline-1,4'-piperidinium] iodide



C38 H46 Cl2 I N3 O3; Mol wt: 790.6054

ACTION – The most potent NK₁ receptor antagonist from a series of spiro-substituted piperidines and salts thereof, as demonstrated *in vitro* (IC₅₀ = 1.9 nM for inhibition of substance P-induced guinea pig ileum contractions) and *in vivo* (ID₅₀ = 24 µg/kg i.v. for inhibition of [Sar⁹,Met(O₂)¹¹]-substance P-induced bronchoconstriction in guinea pigs).

SOURCE – Yamanouchi.

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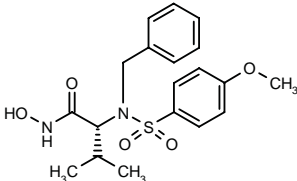
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*Identified compound **234735** (see **230611**) Drug Data Report 1996, 018(05): 0403.

TREATMENT OF RDS AND EMPHYSEMA

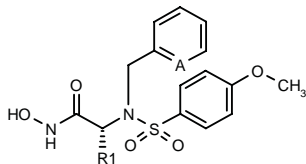
265316¹⁻⁵

2(R)-[N-Benzyl-N-(4-methoxyphenylsulfonyl)amino]-3-methylbutyroxamic acid



C19 H24 N2 O5 S; Mol wt: 392.4736

ACTION – Potent sulfonamide-based hydroxamic acid inhibitor of mouse macrophage metalloelastase (IC₅₀ = 4.9 nM) with potential in the treatment of emphysema. This compound was previously reported to inhibit recombinant human stromelysin (K_i = 0.034 µM). Other compounds from this series include the following:



Compound	R1	A	Formula
265317 ^{4,5}	(S)-CH(Me)Et	CH	C ₂₀ H ₂₆ N ₂ O ₅ S
265318 ¹⁻⁴	i-Pr	N	C ₁₈ H ₂₃ N ₃ O ₅ S

SOURCE – Novartis.

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4. Jeng, A.Y. et al. *Sulfonamide-based hydroxamic acids as potent inhibitors of mouse macrophage metalloelastase*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 39.5.

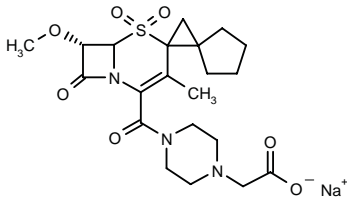
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SYN-1390

265062

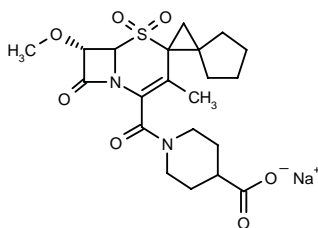
2-[4-[7 (S)-Methoxy-3-methyldispiro[3-cephem-2,1'-cyclopropane-2',1''-cyclopentan]-4-ylcarbonyl]piperazin-1-yl]acetic acid sodium salt

4-[7''(S)-Methoxy-3''-methyl-8''-oxodispiro[cyclopentane-1,1'-cyclopropane-2,4''-[5]thia[1]azabicyclo[4.2.1]-oct[2]en]-2''-ylcarbonyl]-1-piperazineacetic acid sodium salt S,S-dioxide



C21 H28 N3 Na O7 S; Mol wt: 489.5222

ACTION – Reversible human neutrophil elastase (HNE) inhibitor (IC₅₀ = 91 nM) with the ability to protect the lung against HNE-mediated hemorrhage in mice, affording significant protection (53-92%) at a molar ratio of inhibitor:HNE as low as 4:1 administered intranasally at up to 4 h before HNE. Aerosol administration of title compound significantly decreased both elastase concentrations and lung neutrophil counts in the rat agar bead model of *Pseudomonas aeruginosa* chronic lung infection. Another 2-spirocyclopropyl cephem sulfone is:



SYN-1396 [265063]: C21 H27 N2 Na O7 S

SOURCE – Synphar.

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1. Maiti, S.N. et al. (Synphar Laboratories Inc.) *2-Spiro(2'-spirocycloalkyl)cyclopropyl cephalosporin sulfones as antiinflammatory and antidegenerative agents*. EP 733055, JP 97506100, US 5439904, WO 9515966.

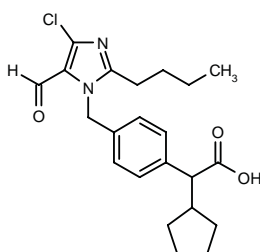
MONOGRAPH – Maiti, S.N. et al. *2-Spirocyclopropyl cephem sulfones: Human neutrophil elastase inhibitors Syn-1390 and Syn-1396*. Drugs Fut 1998, 023(06): 635.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

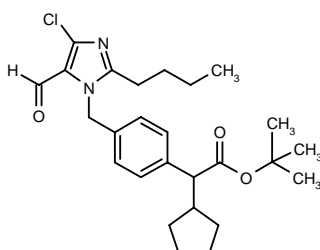
266083

2-[4-(2-Butyl-4-chloro-5-formylimidazol-1-ylmethyl)-phenyl]-2-cyclopentylacetic acid



C22 H27 Cl N2 O3; Mol wt: 402.9193

ACTION – Antihypertensive and antiatherosclerotic agent with selective angiotensin II-antagonist activity, as demonstrated *in vitro* in rabbit aorta strips by an IC_{50} value of 4.6 μ M for inhibition of AII-induced contractions, versus an IC_{50} > 100 μ M for inhibition of KCl-induced contractions; it also inhibits the proliferation of smooth muscle cells. Another compound from this series of phenylacetic acid derivatives is:



266147: C26 H35 Cl N2 O3

SOURCE – Bayer.

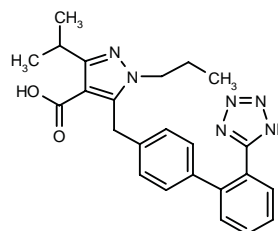
REFERENCES

1. Muller, U. et al. (Bayer AG) *Heterocyclically subst. phenylacetic acid derivs. and their use in medicaments*. US 5776964.

UR-7247

266246

3-Isopropyl-1-propyl-5-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-pyrazole-4-carboxylic acid



C24 H26 N6 O2; Mol wt: 430.5094

ACTION – Antihypertensive agent with a favorable renal hemodynamic profile, an orally active, nonpeptide angiotensin II (AII) AT_1 receptor antagonist. In anesthetized pithed rats, it dose-dependently antagonized the pressor responses to AI, AII and AIII, with a similar effect against all angiotensins at a dose of 1 mg/kg i.v., and it was more effective than losartan. In conscious, sodium-depleted, furosemide-treated rats, the compound produced maximum decreases in blood pressure of 20.4, 27.2 and 45.8 mmHg, respectively, following oral doses of 0.1, 0.3 and 1 mg/kg, the hypotensive effect lasting for over 24 h; it was more effective than losartan and enalapril and no tachycardia was observed. UR-7247 (1 mg/kg i.v.) also increased renal blood flow in anesthetized rabbits without significantly altering blood pressure.

SOURCE – Uriach.

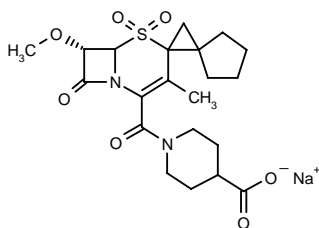
REFERENCES

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2. Cavalcanti, F.L. et al. *Antihypertensive and renal effect of UR-7247, an orally active nonpeptide AT_1 receptor antagonist*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 38.46.

3. Fernández de Arriba, A. et al. *Pharmacological characterization of a novel and highly potent nonpeptide AT_1 receptor antagonist, UR-7247, in vitro*. Br J Pharmacol 1998, 124(Suppl.): Abst 107P.

4. Nieto, C. et al. *Disposition of 6 new non-peptide angiotensin II receptor antagonists in rats*. Methods Find Exp Clin Pharmacol 1996, 18(Suppl. B): Abst P-105.



SYN-1396 [265063]: C21 H27 N2 Na O7 S

SOURCE – Synphar.

REFERENCES

1. Maiti, S.N. et al. (Synphar Laboratories Inc.) *2-Spiro(2'-spirocycloalkyl)cyclopropyl cephalosporin sulfones as antiinflammatory and antidegenerative agents*. EP 733055, JP 97506100, US 5439904, WO 9515966.

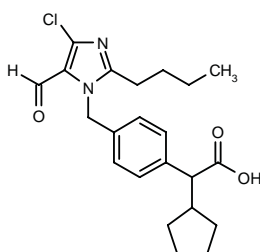
MONOGRAPH – Maiti, S.N. et al. *2-Spirocyclopropyl cephem sulfones: Human neutrophil elastase inhibitors Syn-1390 and Syn-1396*. Drugs Fut 1998, 023(06): 635.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

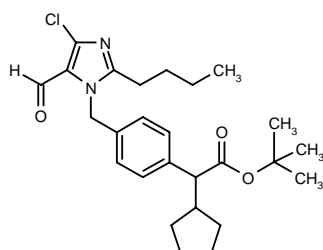
266083

2-[4-(2-Butyl-4-chloro-5-formylimidazol-1-ylmethyl)-phenyl]-2-cyclopentylacetic acid



C22 H27 Cl N2 O3; Mol wt: 402.9193

ACTION – Antihypertensive and antiatherosclerotic agent with selective angiotensin II-antagonist activity, as demonstrated *in vitro* in rabbit aorta strips by an IC₅₀ value of 4.6 μM for inhibition of AII-induced contractions, versus an IC₅₀ > 100 μM for inhibition of KCl-induced contractions; it also inhibits the proliferation of smooth muscle cells. Another compound from this series of phenylacetic acid derivatives is:



266147: C26 H35 Cl N2 O3

SOURCE – Bayer.

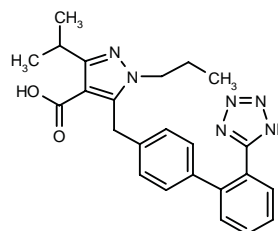
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1. Muller, U. et al. (Bayer AG) *Heterocyclically subst. phenylacetic acid derivs. and their use in medicaments*. US 5776964.

UR-7247

266246

3-Isopropyl-1-propyl-5-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-pyrazole-4-carboxylic acid



C24 H26 N6 O2; Mol wt: 430.5094

ACTION – Antihypertensive agent with a favorable renal hemodynamic profile, an orally active, nonpeptide angiotensin II (AII) AT₁ receptor antagonist. In anesthetized pithed rats, it dose-dependently antagonized the pressor responses to AI, AII and AIII, with a similar effect against all angiotensins at a dose of 1 mg/kg i.v., and it was more effective than losartan. In conscious, sodium-depleted, furosemide-treated rats, the compound produced maximum decreases in blood pressure of 20.4, 27.2 and 45.8 mmHg, respectively, following oral doses of 0.1, 0.3 and 1 mg/kg, the hypotensive effect lasting for over 24 h; it was more effective than losartan and enalapril and no tachycardia was observed. UR-7247 (1 mg/kg i.v.) also increased renal blood flow in anesthetized rabbits without significantly altering blood pressure.

SOURCE – Uriach.

REFERENCES

1. Almansa, C. et al. (J. Uriach & Cia., SA) *New pyrazole derivs. as angiotensin II antagonists*. EP 721454, ES 2105939, JP 97504804, WO 9604273.

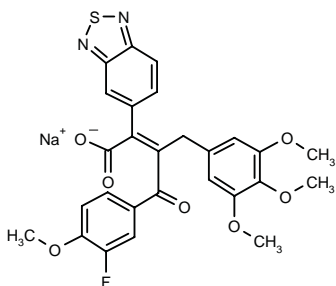
2. Cavalcanti, F.L. et al. *Antihypertensive and renal effect of UR-7247, an orally active nonpeptide AT₁ receptor antagonist*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 38.46.

3. Fernández de Arriba, A. et al. *Pharmacological characterization of a novel and highly potent nonpeptide AT₁ receptor antagonist, UR-7247, in vitro*. Br J Pharmacol 1998, 124(Suppl.): Abst 107P.

4. Nieto, C. et al. *Disposition of 6 new non-peptide angiotensin II receptor antagonists in rats*. Methods Find Exp Clin Pharmacol 1996, 18(Suppl. B): Abst P-105.

EMD-122946***266360****256219** (as free acid)

2-(2,1,3-Benzothiadiazol-5-yl)-4-(3-fluoro-4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-2(Z)-butenoic acid sodium salt



C27 H22 F N2 Na O7 S; Mol wt: 560.5318

ACTION – Highly potent, selective, orally active ET_A receptor antagonist, with high binding affinity for the receptor ($IC_{50} = 0.032$ nM), high selectivity relative to ET_B receptors ($IC_{50} = 160$ nM) and excellent functional antagonist activity, as measured against ET-1-induced contractions in isolated rabbit aortic rings ($pA_2 = 9.5$). It inhibited the pressor response to ET-1 in pithed rats ($ED_{50} = 0.3$ mg/kg p.o.), whereas it had no effect against the depressor response to ET-1. In conscious spontaneously hypertensive rats, EMD-122946 reduced blood pressure gradually and persistently (> 24 h) with an ED_{50} of 0.06 mg/kg p.o., without affecting heart rate or motor activity; the compound also gave an ED_{50} of 0.06 mg/kg p.o. in DOCA-salt hypertensive rats. High oral bioavailability (30-70%) and rapid absorption were observed in rats and cynomolgus monkeys.

SOURCE – Merck KGaA.

REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) 2,1,3-Benzothia(oxa)diazole derivs. having an endothelin receptor antagonistic effect. DE 19607096, WO 9730982.
2. Mederski, W.W.K.R. et al. 3. Endothelin antagonists: Discovery of EMD 122946, a highly potent and orally active ET_A selective antagonist. Bioorg Med Chem Lett 1998, 8(13): 1771.

*Identified compound **256219** (see **255072**) Drug Data Report 1997, 019(11): 0986.

ACTION – Potent, orally active, reversible and competitive dual endothelin ET_A/ET_B receptor antagonist, as demonstrated in binding studies ($K_i = 0.034$ and 0.104 nM, respectively, for ET_A and ET_B receptors) and in functional assays, inhibiting agonist-induced contractions in rabbit iliac artery (ET_A) and pulmonary artery (ET_B) with respective pA_2 values of 9.7 and 10.14. ET-1-induced lethality in mice was prevented by J-104132 ($ED_{50} = 0.045$ i.v., $ED_{50} = 0.35$ - 0.48 mg/kg p.o.), and it also inhibited the ET-1-induced pressor response ($ED_{50} = 0.06$ mg/kg i.v., $ED_{50} = 0.37$ mg/kg p.o.). It rapidly reduced mean arterial blood pressure in DOCA-salt hypertensive rats to normotensive levels at doses of 0.3 mg/kg i.v. or 1 and 3 mg/kg p.o., effects lasting for over 6 h with no significant change in heart rate; chronic (10 days) administration of J-104132 (10 mg/kg p.o. b.i.d.) significantly lowered MAP, with greater and more sustained effects on day 10 compared to day 1, whereas enalapril was inactive and the effect of felodipine was less sustained. J-104132 is currently undergoing phase I trials.

SOURCES – Banyu; Merck & Co.

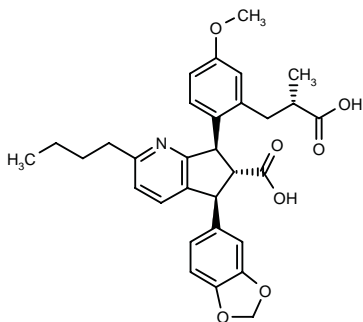
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2. Ishikawa, K. et al. (Banyu Pharmaceutical Co., Ltd.) Endothelin antagonistic heteroaromatic ring-fused cyclopentene derivs. EP 714897, US 5389620, US 5714479, WO 9505374.
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4. Gabel, R. et al. Antihypertensive efficacy of J-104,132 (L-753,037), a potent, orally-active, mixed ET_A/ET_B endothelin receptor antagonist, in conscious, DOCA/salt hypertensive rats. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 38.20.
5. Niiyama, K. et al. A potent, orally active, most balanced ET_A/ET_B dual endothelin receptor antagonist. Discovery of J-104132. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.297.
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7. Nishikibe, M. et al. Pharmacology of J-104,132, a potent, orally-active, mixed ET_A/ET_B endothelin receptor antagonist. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.16.
8. Merck & Co. and Banyu collaborate on development of ET antagonist. Daily Essentials 1998, June 17.

J-104132**266320**

(5*S*,6*R*,7*R*)-2-Butyl-7-[2-[2(*S*)-carboxypropyl]-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6-carboxylic acid

L-753037

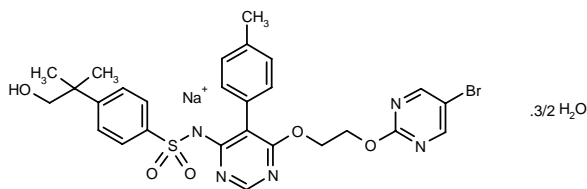


C31 H33 N O7; Mol wt: 531.6017

TA-0201**248767**

N-[6-[2-(5-Bromopyridin-2-yloxy)ethoxy]-5-(4-methylphenyl)pyrimidin-4-yl]-4-[1-(hydroxymethyl)-1-methylethyl]benzenesulfonamide monosodium salt sesquihydrate

T-0201



C27 H27 Br N5 Na O5 S . 3/2 H2 O; Mol wt: 663.5228

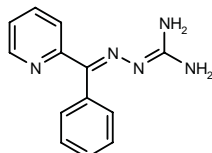
SOURCE – Pfizer.

REFERENCES

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265273

*N*²-[1-Phenyl-1-(2-pyridyl)methyleneamino]guanidine



C13 H13 N5; Mol wt: 239.2807

ACTION – An inhibitor of Na⁺/H⁺ exchange (45% inhibition at 30 μM), a representative compound within a series of guanidine derivatives.

SOURCE – Takeda.

REFERENCES

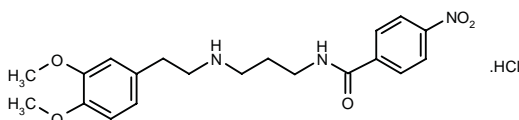
1. Shiroishi, M. et al. (Takeda Chemical Industries, Ltd.) *Aminoguanidinehydrazones derivs., their preparation method and agents*. JP 98114744.

ANTIARRHYTHMIC DRUGS

SB-237376*

237630

N-[3-[2-(3,4-Dimethoxyphenyl)ethylamino]propyl]-4-nitrobenzamide hydrochloride



C20 H25 N3 O5 . HCl ; Mol wt: 423.8944

ACTION – Antiarrhythmic agent with dual potassium and calcium channel-blocking properties, as demonstrated in guinea pig ventricular myocytes by its ability to inhibit the rapid component of the delayed rectifier K⁺ current and the L-type Ca²⁺ current (EC₅₀ = 0.052 and 4.37 μM, respectively). SB-237376 exerted relatively frequency-independent effects on action potential duration at 90% repolarization (APD₉₀), and in dog Purkinje fibers it did not induce early afterdepolarizations and prevented early afterdepolarizations induced by dofetilide, indicating low proarrhythmic potential. In methoxamine-treated rabbits, it induced similar Q-T interval prolongation (35% at 10 μg/kg/min) compared to class III agents, but did not induce torsade de pointes. The compound displayed potent activity against atrial and ventricular fibrillation and ventricular tachycardia in dog and pig models, associated with an increase in atrial and ventricular refractoriness. It appears to offer benefits over class III antiarrhythmic agents, and is currently in phase I evaluation.

SOURCE – SmithKline Beecham.

REFERENCES

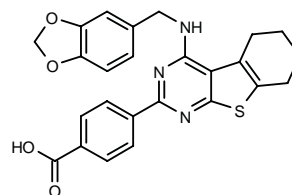
1. Nadler, G.M.M.G. and Martin, M.J.R. (SmithKline Beecham plc) *Nitro-benzamides useful as anti-arrhythmic agents*. EP 788474, FR 2726267, JP 98508013, WO 9613479.
2. Faivre, J.F. et al. *SB-237376, a new antiarrhythmic compound with a dual potassium and calcium channel blocking action has improved antiarrhythmic properties*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 28.16.
3. Gout, B. et al. *In vivo efficacy of SB-237376, a dual potassium and calcium channel antagonist, against atrial and ventricular arrhythmias*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 28.17.
4. *SmithKline Beecham provides update on product pipeline and future directions*. Daily Essentials 1998, April 21.
5. SmithKline Beecham Annual Report 1996.

*Identified compound **237630** Drug Data Report 1996, 018(08): 0711.

HEART FAILURE THERAPY

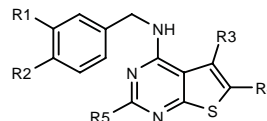
264889

4-[4-(1,3-Benzodioxol-5-ylmethylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl]benzoic acid



C25 H21 N3 O4 S; Mol wt: 459.5239

ACTION – Agent for the treatment of cardiovascular disorders, particularly heart failure, and erectile dysfunction, a specific inhibitor of cGMP phosphodiesterase (PDE5). Other specifically claimed compounds from this series of thienopyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
266032		-OCH2O-	H	Me	4-CO2H-Ph	C ₂₂ H ₁₇ N ₃ O ₄ S
266033		-OCH2O-	Me	Me	4-CO2H-Ph	C ₂₃ H ₁₉ N ₃ O ₄ S
266034		-OCH2O-	H	Cl	4-CO2H-Ph	C ₂₁ H ₁₄ ClN ₃ O ₄ S
266035	Cl	OMe	-(CH2)4-		4-CO2H-Ph	C ₂₅ H ₂₂ ClN ₃ O ₃ S
266036		-OCH2O-	-(CH2)4-		4-CO2H-1-Pip	C ₂₄ H ₂₆ N ₄ O ₄ S
266037		-OCH2O-	H	Me	4-CO2H-1-Pip	C ₂₁ H ₂₂ N ₄ O ₄ S
266038		-OCH2O-	-(CH2)4-		4-CO2H-cyclohexyl	C ₂₅ H ₂₇ N ₃ O ₄ S

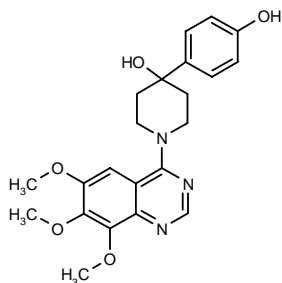
SOURCE – Merck KGaA.

REFERENCES

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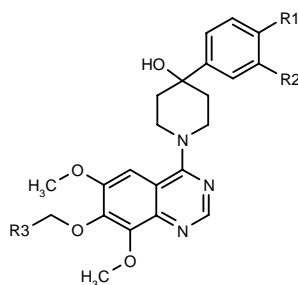
265937

4-[4-Hydroxy-1-(6,7,8-trimethoxyquinazolin-4-yl)piperidin-4-yl]phenol



C22 H25 N3 O5; Mol wt: 411.4555

ACTION – An inhibitor of calmodulin-dependent cGMP phosphodiesterase ($IC_{50} = 0.022 \mu M$ against enzyme from porcine aorta); a representative compound from a series of quinazoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
266529	H	OH	H	$C_{22}H_{25}N_3O_5$
266530	OH	H	Me	$C_{23}H_{27}N_3O_5$

SOURCE – Eisai.

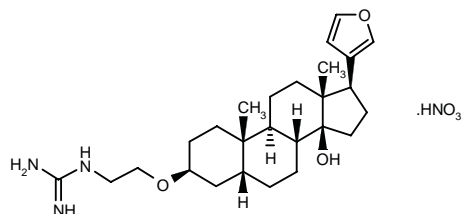
REFERENCES

1. Takase, Y. and Saeki, T. (Eisai Co., Ltd.) *Quinazolines*. JP 98175972.

PST-2107*

206456

17 β -(3-Furyl)-3 β -(2-guanidinoethoxy)-5 β -androstan-14 β -ol nitrate



C26 H41 N3 O3 . H N O3; Mol wt: 506.6398

ACTION – Na^+/K^+ -ATPase inhibitor with inotropic properties; it inhibited the $\alpha 3$ isoform ($K_i = 1.3 \pm 0.04 \mu M$) with 10-fold higher affinity than digoxin, whereas both compounds exhibited similar potency against the $\alpha 1$ isoform ($4 \mu M$). Both compounds increased the force of contraction in isolated electrically paced guinea pig atria ($EC_{50} = 0.39 \pm 0.01$ and $0.38 \pm 0.04 \mu M$, respectively, for PST-2107 and digoxin), but title compound did not

produce arrhythmias up to the maximum concentration tested of $3 \mu M$, whereas digoxin produced arrhythmias at concentrations as low as $0.1 \mu M$. *In vivo* in anesthetized guinea pigs, infusion of PST-2107 (0.16 ml/min i.v.) increased dP/dt by $173 \pm 35\%$, without affecting either heart rate or blood pressure, with a faster onset of inotropic effect and more rapid reversal after discontinuation of infusion compared to digoxin; it showed 3-fold lower inotropic potency compared to digoxin but was less toxic.

SOURCE – Sigma-Tau.

REFERENCES

1. Quadri, L. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Cyclopentanperhydrophenanthren-17 β -(3-furyl)-3-derivs. and pharmaceutical compns. comprising same for the treatment of cardiovascular disorders*. EP 576915, JP 94065284, US 5432169.

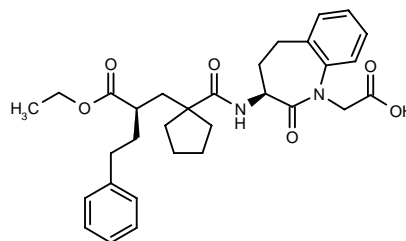
2. Micheletti, R. et al. *Inotropic properties of PST 2107, a novel Na,K-ATPase inhibitor*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 36.73.

*Identified compound **206456** (see **204899**) Drug Data Report 1994, 016(04): 0337.

SLV-306*

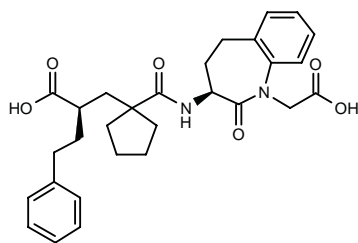
242925

2-[3(S)-[1-[2(R)-(Ethoxycarbonyl)-4-phenylbutyl]-cyclopentan-1-ylcarboxamido]-2-oxo-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl]acetic acid



C31 H38 N2 O6; Mol wt: 534.6492

ACTION – Orally active dual inhibitor of neutral endopeptidase (NEP) and endothelin-converting enzyme (ECE) that is metabolized to the active compound **KC-12615**; KC-12615 displays nanomolar potency against NEP and micromolar potency against ECE. In conscious rats, orally administered SLV-306 and i.v. KC-12615 both produced dose-dependent diuresis and natriuresis. In DOCA-salt hypertensive rats, SLV-306 (10 mg/kg) and KC-12615 (30 mg/kg), both given i.v., demonstrated significant antihypertensive activity, and pretreatment with SLV-306 (10 mg/kg i.d.) and KC-12615 (10 mg/kg i.v.) markedly inhibited the pressor response to big endothelin in anesthetized rats. In a model of congestive heart failure (CHF) in rats with an aortic stenosis, SLV-306 (30 mg/kg/day p.o. for 12 weeks) significantly reduced cardiac hypertrophy and signs of pulmonary congestion. This profile suggests potential in the treatment of chronic CHF.



KC-12615 [242585]:** C₂₉ H₃₄ N₂ O₆

SOURCE – Solvay.

REFERENCES

1. Rozsa, S. et al. (Solvay SA) *Drugs for increasing gastrointestinal blood supply*. DE 19638020, EP 830863, JP 98101565.
2. Waldeck, H. et al. (Kali-Chemie AG) *Benzazepin-, benzoxazepin- and benzothiazepin-N-acetic acid-derivs., their preparation and their pharmaceutical compsns.* CA 2172354, EP 733642, JP 96269011, US 5677297.
3. Meil, J. et al. *In-vivo results with SLV 306 and orally active inhibitor of NEP and ECE*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.25.
4. Meil, J. et al. *Pharmacology of the active metabolite of SLV 306 - a mixed inhibitor of NEP and ECE*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.22.

*Identified compound **242925** (see **242585**) Drug Data Report 1997, 019(02): 0136.

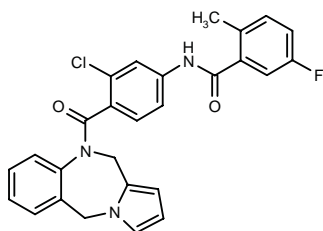
Identified compound **242585 Drug Data Report 1997, 019(02): 0136.

VPA-985*

224116

N-[3-Chloro-4-(10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-10-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide

WAY-VPA-985



C₂₇ H₂₁ Cl F N₃ O₂; Mol wt: 473.9329

ACTION – Potent, selective and orally active vasopressin V₂ receptor antagonist, as demonstrated in binding studies using human (IC₅₀ = 1.2 and 230 nM, respectively, for V₂ and V_{1a} receptors) and rat receptors (IC₅₀ = 2.3 and 340 nM, respectively, for V₂ and V_{1a} receptors), undergoing phase II testing for the treatment of conditions characterized by water retention and inappropriate arginine vasopressin (AVP) secretion such as congestive heart failure (CHF), liver cirrhosis, nephrotic syndrome and hyponatremia. The compound showed aquaretic and V₂ receptor-antagonist effects *in vivo* in several animal models following oral administration. In a double-blind, randomized, placebo-controlled trial in patients with CHF and deprived of fluids, oral doses of 30, 75 and 150 mg were associated with increases in urine flow and serum sodium levels, as well as reductions in urinary osmolality.

SOURCE – Wyeth-Ayerst.

REFERENCES

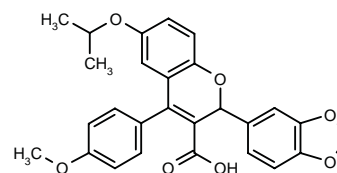
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3. Reich, M.F. et al. (American Cyanamid Co.) *Tricyclic diazepine vasopressin antagonists and oxytocin antagonists*. US 5733905.
4. Reich, M.F. et al. (American Cyanamid Co.) *Tricyclic diazepine vasopressin antagonists and oxytocin antagonists*. US 5736540.
5. Abraham, W.T. et al. *Effects of an oral, nonpeptide, selective V₂ receptor vasopressin antagonist in patients with chronic heart failure*. J Am Coll Cardiol 1997, 29(2, Suppl. A): Abst 727-1.
6. Albright, J.D. et al. *5-Fluoro-2-methyl-N-[4-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl]-3-chlorophenyl]benzamide (VPA-985): An orally active arginine vasopressin antagonist with selectivity for V₂ receptors*. J Med Chem 1998, 41(14): 2442.
7. Albright, J.D. et al. *Arginine vasopressin (AVP) antagonists*. Pyrrolo [2,1-*c*][1,4]benzodiazepines. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 018.
8. Chan, P.S. et al. *Pharmacological characterization of VPA-985, a potent nonpeptidic orally-active and selective vasopressin (AVP) V₂ receptor antagonist*. J Am Soc Nephrol 1998, Abst A0081.
9. Park, C.H. et al. *In vitro pharmacology of VPA-985, a non-peptide V₂ selective vasopressin antagonist*. J Am Soc Nephrol 1998, Abst A0120.
10. American Home Products Corp. Analyst Presentation (April 10, New York) 1995.
11. American Home Products Corp. Product Pipeline 1998, Aug 26.

*Identified compound **224116** (see **221198**) Drug Data Report 1995, 017(08): 0725.

MISCELLANEOUS CARDIOVASCULAR DRUGS

263356

2-(1,3-Benzodioxol-5-yl)-6-isopropoxy-4-(4-methoxyphenyl)-2*H*-1-benzopyran-3-carboxylic acid



C₂₇ H₂₄ O₇; Mol wt: 460.4796

ACTION – Agent for the treatment of cardiovascular disorders, an endothelin receptor antagonist with higher affinity for ET_A receptors (IC₅₀ = 0.89 nM for displacement of [¹²⁵I]-ET-1 binding in rat aortic smooth muscle) than ET_B receptors (IC₅₀ = 180 nM for displacement of [¹²⁵I]-ET-3 binding to porcine ET_B receptors cloned in COS-7 cells). *In vivo*, compound was found to increase blood flow in a rat model of peripheral circulatory insufficiency at 30 mg/kg p.o.

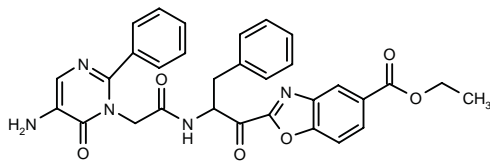
SOURCE – Shionogi.

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1. Ishizuka, N. et al. (Shionogi & Co. Ltd.) *Chromene-3-carboxylate derivs*. WO 9808836.

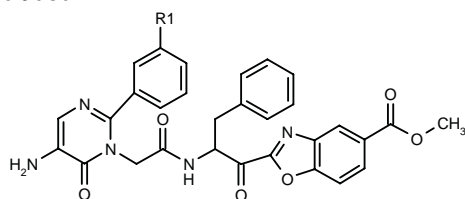
265122

2-[2-[2-(5-Amino-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)acetamido]-3-phenylpropionyl]benzoxazole-5-carboxylic acid ethyl ester



C31 H27 N5 O6; Mol wt: 565.5833

ACTION – Agent for the treatment of cardiovascular disorders with potent chymase-inhibitory activity ($K_i = 0.002 \mu\text{M}$ against human cardiac chymase). Within this series of heterocyclic amide derivatives, the following are also included:



Compound	R1	Formula
266115	OMe	$\text{C}_{31}\text{H}_{27}\text{N}_5\text{O}_7$
266116	NH2	$\text{C}_{30}\text{H}_{26}\text{N}_6\text{O}_6$

SOURCE – Yoshitomi.

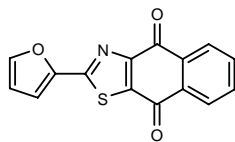
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1. Akahoshi, F. et al. (Green Cross Corp.) *Novel heterocyclic amide cpds. and medicinal uses thereof*. WO 9818794.

INO-5042

266245

2-(2-Furyl)-4,9-dihydronaphtho[2,3-*d*]thiazole-4,9-dione



C15 H7 N O3 S; Mol wt: 281.2903

ACTION – Venotropic agent with good selectivity for veins relative to arteries, thought to act as an antagonist of the EP_4 receptor in venous smooth muscle cells or/and by inhibiting PGE_2 synthesis by venous wall; it shows no affinity for adrenergic, angiotensin, bradykinin, histamine, leukotriene, 5-HT or thromboxane receptors. Title compound produced concentration-dependent (10-300 nM) increases in contractile force in isolated rabbit saphenous vein rings precontracted with KCl, norepinephrine or 5-HT, but it had no effect on basal tension; it also potentiated the contractile response to submaximal electrical stimulation. Potentially useful for the treatment of venous insufficiency.

SOURCE – Innothra.

REFERENCES

1. Desquand-Billiard, S. et al. *Venoselective contraction induced by INO 5042 on isolated rabbit vessels*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 37.116.

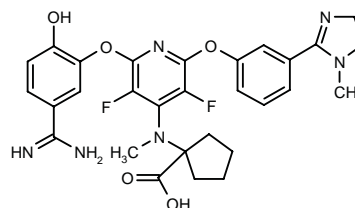
2. Hanf, R. et al. *INO 5042 contracts rabbit saphenous vein through inhibition of a PGE_2 mediated vasodilation*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 37.118.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

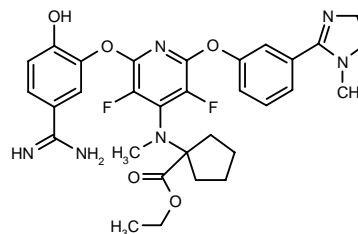
263850

1-[*N*-[2-(5-Amidino-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydroimidazol-2-yl)phenoxy]pyridin-4-yl]-*N*-methylamino]cyclopentane-1-carboxylic acid



C29 H30 F2 N6 O5; Mol wt: 580.5890

ACTION – Anticoagulant with the ability to selectively inhibit human factor Xa and thrombin. It was reported to be active in a model of venous thrombosis in rats. Within this series of specifically claimed benzamidine derivatives, the following are also included:



265753: C31 H34 F2 N6 O5

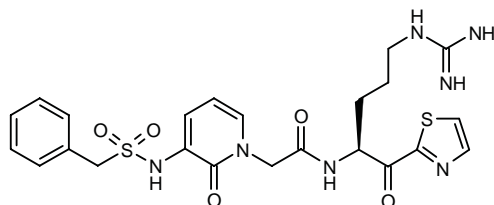
SOURCE – Schering AG.

REFERENCES

1. Kochanny, M. et al. (Schering AG) *Benzamidine derivs. substd. by cyclic amino acid or cyclic hydroxy acid derivs. and their use as anti-coagulants*. WO 9811094.

264855

2-[N^α -[2-[3-(Benzylsulfonamido)-2-oxo-1,2-dihydropyridin-1-yl]acetyl]-L-arginyl]thiazole

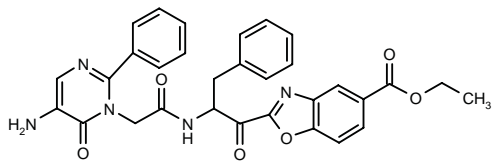


C23 H27 N7 O5 S2; Mol wt: 545.6423

ACTION – Anticoagulant, an inhibitor of factor Xa and thrombin ($\text{IC}_{50} = 3$ and 8 nM , respectively). Other heterocyclic compounds include the following:

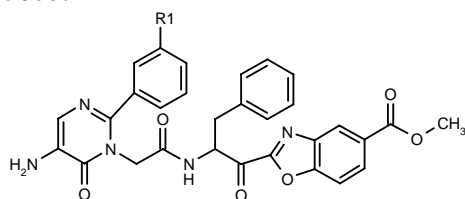
265122

2-[2-[2-(5-Amino-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)acetamido]-3-phenylpropionyl]benzoxazole-5-carboxylic acid ethyl ester



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SOURCE – Yoshitomi.

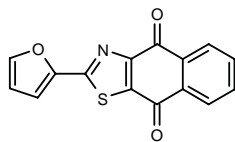
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INO-5042

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SOURCE – Innothra.

REFERENCES

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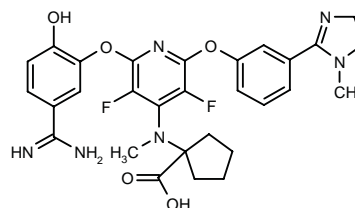
2. Hanf, R. et al. *INO 5042 contracts rabbit saphenous vein through inhibition of a PGE_2 mediated vasodilation*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 37.118.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

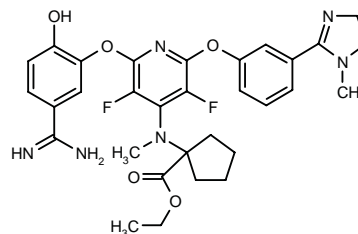
263850

1-[*N*-[2-(5-Amidino-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydroimidazol-2-yl)phenoxy]pyridin-4-yl]-*N*-methylamino]cyclopentane-1-carboxylic acid



C29 H30 F2 N6 O5; Mol wt: 580.5890

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265753: C31 H34 F2 N6 O5

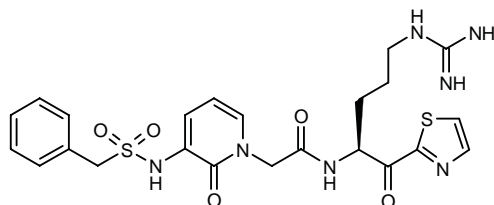
SOURCE – Schering AG.

REFERENCES

1. Kochanny, M. et al. (Schering AG) *Benzamidine derivs. substd. by cyclic amino acid or cyclic hydroxy acid derivs. and their use as anti-coagulants*. WO 9811094.

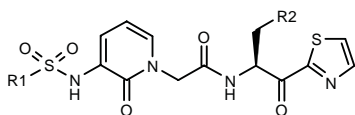
264855

2-[N^α -[2-[3-(Benzylsulfonamido)-2-oxo-1,2-dihydropyridin-1-yl]acetyl]-L-arginyl]thiazole



C23 H27 N7 O5 S2; Mol wt: 545.6423

ACTION – Anticoagulant, an inhibitor of factor Xa and thrombin ($\text{IC}_{50} = 3$ and 8 nM , respectively). Other heterocyclic compounds include the following:



Compound	R1	R2	Formula
266268	4-Cl-PhCH2	CH2CH2NHC(=NH)NH2	C ₂₃ H ₂₆ ClN ₇ O ₅ S ₂
266269	6-Cl-2-Naph-CH2	CH2CH2NHC(=NH)NH2	C ₂₇ H ₂₈ ClN ₇ O ₅ S ₂
266270	4-Br-Ph	CH2CH2NHC(=NH)NH2	C ₂₂ H ₂₄ BrN ₇ O ₅ S ₂
266271	3,4-(Cl)2-PhCH2	CH2CH2NHC(=NH)NH2	C ₂₃ H ₂₅ Cl ₂ N ₇ O ₅ S ₂
266272	4-Cl-PhCH2	(CH2)3NH2	C ₂₃ H ₂₆ ClN ₅ O ₅ S ₂
266273	4-Cl-PhCH2	3-indolyl	C ₂₈ H ₂₄ ClN ₅ O ₅ S ₂
266274	4-Pyr-CH2	CH2CH2NHC(=NH)NH2	C ₂₂ H ₂₆ N ₈ O ₅ S ₂

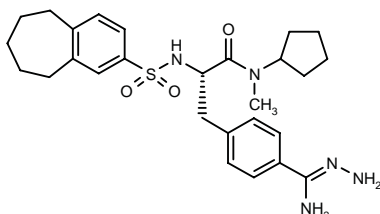
SOURCE – COR Therapeutics.

REFERENCES

1. Zhu, B.-Y. and Scarborough, R.M. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors*. WO 9816547.

265751

3-[4-(*N*²-Aminoamidino)phenyl]-*N*-cyclopentyl-*N*-methyl-2(*S*)-(6,7,8,9-tetrahydrobenzocyclohepten-2-yl)sulfonamido)propionamide



C27 H37 N5 O3 S; Mol wt: 511.6873

ACTION – Potent and selective human thrombin inhibitor ($K_i = 0.045$ nM; K_i trypsin = 5.5 μ M). Although title compound exhibited enhanced potency and selectivity for thrombin with respect to the lead compound LB-30057, it exhibited relatively lower oral absorption.

SOURCE – LG Chemical.

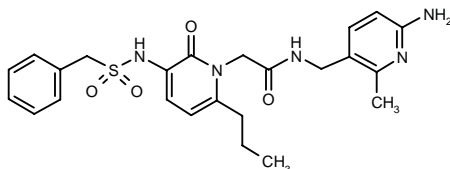
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L-375052

266359

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[3-(benzylsulfonamido)-2-oxo-6-propyl-1,2-dihydropyridin-1-yl]-acetamide



C24 H29 N5 O4 S; Mol wt: 483.5901

ACTION – Thrombin inhibitor derived from L-374087 that retains the excellent potency ($K_i = 0.85$ nM), selectivity (K_i trypsin = 1400 nM) and anticoagulant/antithrombotic efficacy of the latter but shows improved oral absorption in rats and dogs. In the rat ferric chloride model of arterial thrombosis, the incidence of occlusion was 1 of 6 at 10 μ g/kg/min versus 0 of 6 for L-374087 at the same dose. In dogs, it gave higher peak plasma levels than L-374087 following doses of 5 mg/kg p.o., as well as a longer duration of action ($t_{1/2} = 189$ min vs. 151 min for L-374087); in rats, peak concentrations of 250 nM were attained following 10 mg/kg p.o., whereas L-374087 was undetectable in rat plasma following a dose of 20 mg/kg p.o.

SOURCE – Merck & Co.

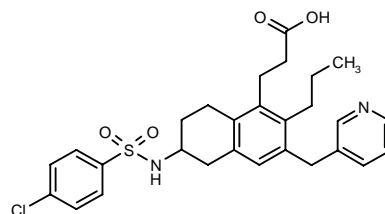
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2. Sanderson, P.E. et al. (Merck & Co., Inc.) *Pyridinone-thrombin inhibitors*. EP 835109, WO 9701338.
3. Isaacs, R.C.A. et al. *C6 modification of the pyridinone core of thrombin inhibitor L-374,087 as a means of enhancing its oral absorption*. Bioorg Med Chem Lett 1998, 8(13): 1719.

ANTIPLATELET THERAPY

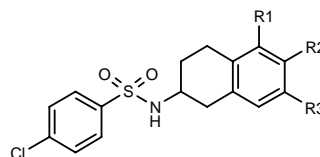
264967^{1,2}

3-[6-(4-Chlorophenylsulfonamido)-2-propyl-3-(3-pyridylmethyl)-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid



C28 H31 Cl N2 O4 S; Mol wt: 527.0819

ACTION – Potent dual thromboxane receptor antagonist and TxA_2 synthase inhibitor, giving an IC_{50} for inhibition of TxA_2 synthase in human whole blood of 0.64 μ M and a pA_2 value of 8.4 against U-46619-induced contractions of isolated rabbit saphenous vein. It inhibited U-46619-induced human platelet aggregation with an IC_{50} value of 0.063 μ M. In conscious rats, when given orally at a dose of 10 mg/kg, it provided complete and long-lasting (> 6 h) TxA_2 synthase inhibition and thromboxane receptor blockade. Other related tetrahydronaphthalene derivatives are:



Compound	R1	R2	R3	Formula
231221 ^{1,3}	CH2CH2CO2H	H	3-Pyr-CH2	C ₂₅ H ₂₅ ClN ₂ O ₄ S
264969 ^{1,2}	(E)-CH=CH-(CH2)3CO2H	3-Pyr-CH2	H	C ₂₈ H ₂₉ ClN ₂ O ₄ S

SOURCE – Servier.

REFERENCES

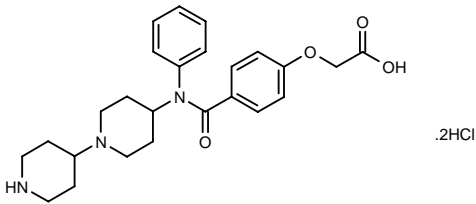
1. Lavielle, G. et al. (ADIR et Cie.) 1,2,3,4-Tetrahydronaphthalene, chroman and thiochroman derivs. as antithrombotic agents. CA 2118102, EP 648741, FR 2711139, JP 95188155.

2. Cimetière, B. et al. New tetrahydronaphthalene derivatives as combined thromboxane receptor antagonists and thromboxane synthase inhibitors. Bioorg Med Chem Lett 1998, 8(11): 1381.

3. Cimetière, B. et al. Synthesis and biological evaluation of new tetrahydronaphthalene derivatives as thromboxane A₂ receptor antagonists and combined antago-nists/synthase inhibitors. 210th ACS Natl Meet (Aug 20-24, Chicago) 1995, Abst MEDI 062.

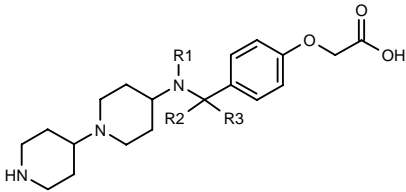
264875

2-[4-[N-Phenyl-N-[1-(4-piperidyl)piperidin-4-yl]carbamoyl]-phenoxy]acetic acid dihydrochloride



C25 H31 N3 O4 . 2 HCl; Mol wt: 510.4587

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 9.1 nM against [³H]-BIBU-52 binding in human platelets) proven to inhibit collagen-induced aggregation of human platelets with an IC₅₀ of 31 nM. Other specifically claimed compounds from this series of 1-(4-piperidyl)piperidines include the following:



Compound	R1	R2	R3	Formula
267036	4-MeO-PhCH2	-O-		C ₂₇ H ₃₅ N ₃ O ₅
267037	CH2Ph	-O-		C ₂₆ H ₃₃ N ₃ O ₄
267038	i-Bu	-O-		C ₂₃ H ₃₅ N ₃ O ₄
267039	4-Pyr-CH2	-O-		C ₂₅ H ₃₂ N ₄ O ₄
267040	4-F-PhCH2	-O-		C ₂₆ H ₃₂ FN ₃ O ₄
267041	cyclohexyl	-O-		C ₂₅ H ₃₇ N ₃ O ₄
267042	4-MeO-PhCH2	H	H	C ₂₇ H ₃₇ N ₃ O ₄
267043	CH2Ph	H	H	C ₂₆ H ₃₅ N ₃ O ₃
267044	3-Pyr-CH2	-O-		C ₂₅ H ₃₂ N ₄ O ₄

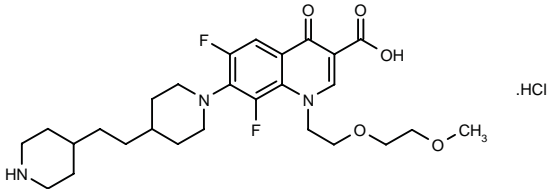
SOURCE – Boehringer Ingelheim.

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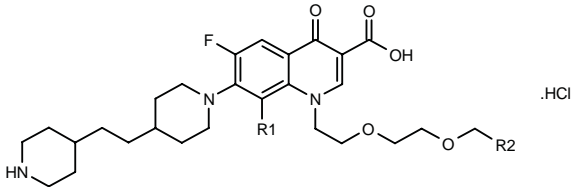
265255

6,8-Difluoro-1-[2-(2-methoxyethoxy)ethyl]-7-[4-[2-(4-piperidiny)ethyl]piperidin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid hydrochloride



C27 H37 F2 N3 O5 . HCl; Mol wt: 558.0622

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 2.1 nM) proven to inhibit ADP-induced aggregation of human platelet-rich plasma (PRP) with an IC₅₀ of 63 nM. Other compounds from this series of pyridone-3-carboxylic acid derivatives include the following:



Compound	R1	R2	Formula
265892	H	Me	C ₂₇ H ₃₈ FN ₃ O ₅ .HCl
265893	H	CH2CH2OMe	C ₂₉ H ₄₂ FN ₃ O ₆ .HCl
265894	F	CH2CH2OMe	C ₂₉ H ₄₁ F ₂ N ₃ O ₆ .HCl

SOURCE – Wakunaga.

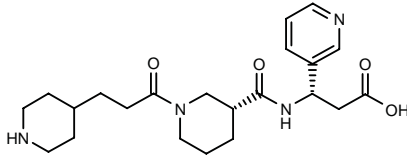
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1. Kuramoto, Y. et al. (Wakunaga Pharmaceutical Co., Ltd.) Novel pyridone carboxylic acid derivs. or their salts and medicines containing them. JP 98130241.

RWJ-53308

266322

3(S)-[1-[3-(4-Piperidiny)propionyl]-3(R)-piperidiny]-carboxamido]-3-(3-pyridyl)propionic acid



C22 H32 N4 O4; Mol wt: 416.5188

ACTION – Potent fibrinogen (gpIIb/IIIa) receptor antagonist (IC₅₀ = 0.3 ± 0.2 nM for displacement of fibrinogen binding to the human receptor) proven to inhibit *in vitro* aggregation induced by arachidonic acid, ADP, collagen or TRAP-6 in platelet-rich plasma with IC₅₀ values ranging from 0.06 to 0.16 μM. In a phase I study, the compound administered orally (1.0-6.0 mg/kg) inhibited ADP-induced platelet aggregation (51-94% 2 h after administration), slightly prolonging bleeding time at doses of 3.0 and 6.0 mg/kg. Inhibition of collagen-induced platelet aggregation was only observed at the highest dose (51% inhibition). RWJ-53308 was well tolerated and showed a very long half-life (15.8-32.3 h).

SOURCE – R.W. Johnson.

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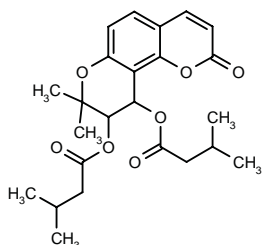
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PJ-1

266607

3-Methylbutyric acid 8,8-dimethyl-2-oxo-2,8,9,10-tetrahydrobenzo[1,2-*b*:3,4-*b'*]dipyran-9,10-diyl ester

3',4'-Diisovalerylkhellactone diester



C24 H30 O7; Mol wt: 430.4940

ACTION – Antiplatelet coumarin derivative isolated from the medicinal herb *Peucedanum japonicum* Thunb. whose antiplatelet effects appear to be due to PAF antagonism and phospholipase A₂ (PLA₂) inhibition. It inhibited PAF- and collagen-induced rabbit platelet aggregation with IC₅₀ values of about 56.3 and 89.4 μM, respectively, whereas it had little effect against arachidonic acid- or thrombin-induced platelet aggregation. It also inhibited ATP release from washed rabbits platelets induced by PAF and collagen. PJ-1 inhibited TxB₂ formation induced by collagen, but not TxB₂ or PGD₂ formation induced by arachidonic acid. The compound also inhibited [³H]-PAF binding to washed platelets with an IC₅₀ of 3.9 μM.

SOURCES – Natl. Chung-Hsing Univ., Taichung (TW); Natl. Taiwan Univ., Taipei (TW).

REFERENCES

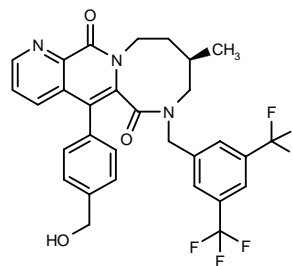
1. Hsiao, G. et al. *Antiplatelet action of 3',4'-diisovalerylkhellactone diester purified from Peucedanum japonicum Thunb.* Biol Pharm Bull 1998, 21(7): 688.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

264368

7-[3,5-Bis(trifluoromethyl)benzyl]-5-[4-(hydroxymethyl)phenyl]-9(*R*)-methyl-7,8,9,10,11,13-hexahydro-6*H*-[1,4]diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione



C30 H25 F6 N3 O3; Mol wt: 589.5335

ACTION – Agent for the treatment of urinary tract disorders such as urinary incontinence and pollakuria with tachykinin, particularly NK₁ (substance P), receptor-antagonist activity. Compound exhibited an IC₅₀ value of 0.84 nM against [¹²⁵I]-BH-substance P binding in human lymphoblast IM-9 cells. *In vivo*, it inhibited the capsaicin-induced increase in guinea pig tracheal vascular permeability with an ID₅₀ value of 2.5 μg/kg i.v.

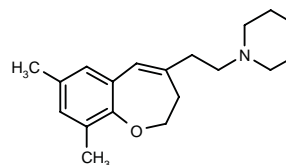
SOURCE – Takeda.

REFERENCES

1. Natsukari, H. et al. (Takeda Chemical Industries, Ltd.) *Cyclic cpds. containing nitrogen, their preparation method and agents*. JP 98109989.

264842

1-[2-(7,9-Dimethyl-2,3-dihydro-1-benzoxepin-4-yl)ethyl]-piperidine



C19 H27 N O; Mol wt: 285.4283

ACTION – Agent for the treatment of urinary tract disorders such as urinary incontinence and pollakuria, proven to significantly reduce the frequency of rhythmic bladder contractions in rats (81% inhibition at 20 mg/kg intraduodenally); at a dose of 10 mg/kg compound was shown to inhibit the micturition reflex. Other compounds from this series of 2,3-dihydrobenzoxepines include the following:

SOURCE – R.W. Johnson.

REFERENCES

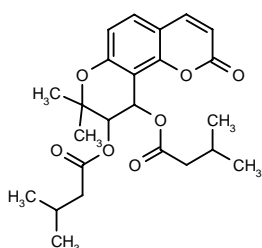
1. Costanzo, M.J. et al. (Ortho Pharmaceutical Corp.) *Carboxamide derivs. of pyrrolidine, piperidine and hexahydroazepine for the treatment of thrombosis disorders*. WO 9741102.
2. Van Hecken, A. et al. *Pharmacodynamics and pharmacokinetics of RWJ-53308, a nonpeptide platelet glycoprotein IIb/IIIa receptor antagonist, in healthy men*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abstr P 47.32.

PJ-1

266607

3-Methylbutyric acid 8,8-dimethyl-2-oxo-2,8,9,10-tetrahydrobenzo[1,2-*b*:3,4-*b'*]dipyran-9,10-diyl ester

3',4'-Diisovalerylkhellactone diester



C24 H30 O7; Mol wt: 430.4940

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SOURCES – Natl. Chung-Hsing Univ., Taichung (TW); Natl. Taiwan Univ., Taipei (TW).

REFERENCES

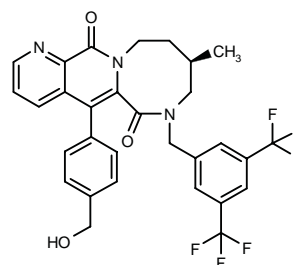
1. Hsiao, G. et al. *Antiplatelet action of 3',4'-diisovalerylkhellactone diester purified from Peucedanum japonicum Thunb.* Biol Pharm Bull 1998, 21(7): 688.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

264368

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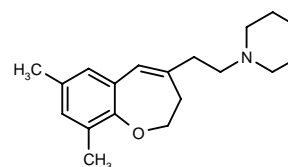
SOURCE – Takeda.

REFERENCES

1. Natsukari, H. et al. (Takeda Chemical Industries, Ltd.) *Cyclic cpds. containing nitrogen, their preparation method and agents*. JP 98109989.

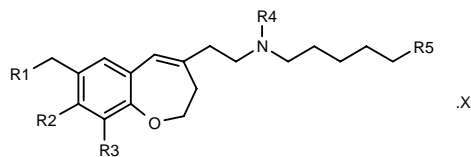
264842

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C19 H27 N O; Mol wt: 285.4283

ACTION – Agent for the treatment of urinary tract disorders such as urinary incontinence and pollakuria, proven to significantly reduce the frequency of rhythmic bladder contractions in rats (81% inhibition at 20 mg/kg intraduodenally); at a dose of 10 mg/kg compound was shown to inhibit the micturition reflex. Other compounds from this series of 2,3-dihydrobenzoxepines include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
266155	H	H	Me	-CH2-			C ₂₀ H ₂₉ NO
266156	H	H	H	-CH2-		HCl	C ₁₉ H ₂₇ NO.HCl
266157	Me	H	H	H	H	HCl	C ₁₉ H ₂₇ NO.HCl
266158	Et	H	H	H	H	HCl	C ₂₀ H ₂₉ NO.HCl
266159	H	Me	H	H	H	HCl	C ₁₉ H ₂₇ NO.HCl
266160	H	Me	H	-CH2-		HCl	C ₂₀ H ₂₉ NO.HCl
266161	-(CH2)2-		H	H	H	HCl	C ₂₀ H ₂₇ NO.HCl
266162	-(CH2)2-		H	-CH2-		HCl	C ₂₁ H ₂₉ NO.HCl

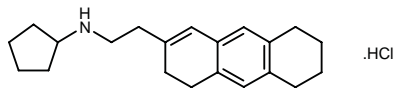
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Morie, T. et al. (Dainippon Pharmaceutical Co., Ltd.) [ω -(2,3-Dihydro-1-benzoxepin-4-yl)alkyl]amine derivs., process for the preparation thereof, and medicinal compsns. containing the same. WO 9816519.

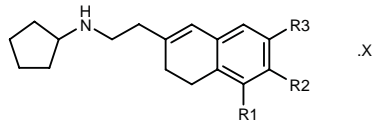
265260

N-Cyclopentyl-N-[2-(3,4,5,6,7,8-hexahydroanthracen-2-yl)ethyl]amine hydrochloride



C21 H29 N . HCl; Mol wt: 331.9280

ACTION – Agent for the treatment of urinary tract disorders such as urinary incontinence and pollakiuria proven to significantly reduce the frequency of rhythmic bladder contractions in rats (57% inhibition at 20 mg/kg intraduodenally); at a dose of 10 mg/kg compound was shown to inhibit the micturition reflex. Other compounds from this series of N-cycloalkylamines include the following:



Compound	R1	R2	R3	X	Formula
266103	F	H	H		C ₁₇ H ₂₂ FN
266104	H	Me	Me		C ₁₉ H ₂₇ N
266105	H	H	H		C ₁₇ H ₂₃ N
266106	H	-CH2CH2O-		HCl	C ₁₉ H ₂₅ NO.HCl

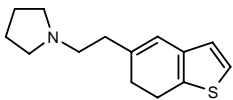
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Morie, T. et al. (Dainippon Pharmaceutical Co., Ltd.) N-Cycloalkyl- ω -(3,4-dihydro-2-naphthalenyl)alkyl]amine derivs. and medicinal compsns. containing them. JP 98120632.

265261

1-[2-(6,7-Dihydrobenzo[b]thiophen-5-yl)ethyl]pyrrolidine



C14 H19 N S; Mol wt: 233.3771

ACTION – Agent for the treatment of urinary tract disorders such as urinary incontinence and pollakiuria proven to inhibit rhythmic bladder contractions in rats with an ED₅₀ value of 4.5 mg/kg administered intraduodenally.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

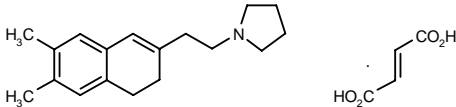
1. Morie, T. et al. (Dainippon Pharmaceutical Co., Ltd.) [ω -(Dihydroheteroaryl)-alkyl]amine derivs. and medicinal compsns. containing them. JP 98120650.

AH-9700*

266319

243775 (as free base)

1-[2-(6,7-Dimethyl-3,4-dihydro-2-naphthalenyl)ethyl]-pyrrolidine fumarate



C18 H25 N . C4 H4 O4; Mol wt: 371.4741

ACTION – Centrally and peripherally acting drug for the treatment of bladder dysfunction, i.e., urinary incontinence and pollakiuria, with high affinity for guinea pig brain σ -receptors (IC₅₀ = 4.32 \pm 0.09 nM for σ_1 receptors), moderate affinity for human recombinant muscarinic receptors (IC₅₀ = 1.81-5.10 μ M for M₁, M₂ and M₃ receptors) and no affinity for other receptors and ion channels tested. It exhibited marked antimicturition reflex activity and moderate spasmolytic activity in bladder smooth muscle of the rat. Title compound (2-20 mg/kg i.d.) dose-dependently increased bladder capacity, measured as prolongation of micturition interval, and the micturition threshold pressure in anesthetized rats. Likewise, the compound decreased both the frequency and the amplitude of rhythmic bladder contractions in rats following both i.v. and i.d. administration, whereas it had no effect on amplitude following i.c.v. administration. In addition, AH-9700 (1-5 mg/kg i.v.) inhibited bladder contractions induced by electrical stimulation of the pelvic nerve.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Kai, N. et al. (Dainippon Pharmaceutical Co., Ltd.) 1- ω -(3,4-Dihydro-2-naphthalenyl)alkyl]cyclic amine derivs., process for producing the same, and medicinal compsn. containing the same. EP 825180, WO 9633169.
2. Kai, N. et al. (Dainippon Pharmaceutical Co., Ltd.) Medicines containing 1- ω -(3,4-dihydro-2-naphthalenyl)alkyl]cyclic amine derivs. JP 98175862.

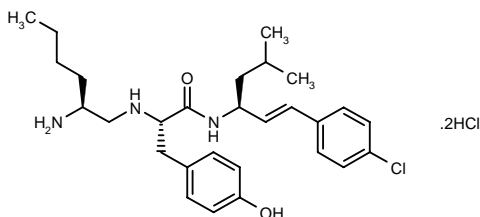
3. Shimizu, I. et al. *Pharmacological profiles of AH-9700, a novel centrally and peripherally acting drug for treatment of urge urinary incontinence and pollakiuria*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.30.

*Identified compound **243775** Drug Data Report 1997, 019(03): 0242.

TREATMENT OF RENAL DISEASES

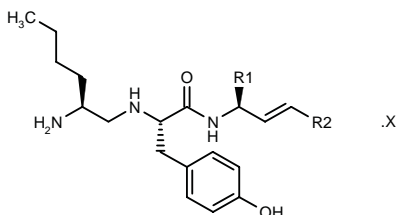
262915

N^α-[2(*S*)-Aminoethyl]-*N*¹-[3-(4-chlorophenyl)-1(*S*)-isobutyl-2(*E*)-propenyl]-L-tyrosinamide dihydrochloride



C₂₈H₄₀Cl₂N₃O₂ · 2 HCl; Mol wt: 559.0178

ACTION – Angiotensin IV receptor agonist, as demonstrated in a binding assay in guinea pig hippocampal membranes using [¹²⁵I]-angiotensin IV as the radioligand (IC₅₀ = 0.53 nM). Potentially useful for increasing renal blood flow, inducing cerebral vasodilatation, improving memory and inhibiting cell proliferation. Other amino compounds include the following:



Compound	R1	R2	X	Formula
266012	CH(Me)Et	4-Me-Ph	2HCl	C ₂₉ H ₄₃ N ₃ O ₂ ·2HCl
266013	i-Bu	4-Pyr	3HCl	C ₂₇ H ₄₀ N ₄ O ₂ ·3HCl
266014	i-Bu	Ph	2HCl	C ₂₈ H ₄₁ N ₃ O ₂ ·2HCl
266015	i-Bu	2-quinolinyl	3HCl	C ₃₁ H ₄₃ N ₄ O ₂ ·3HCl

SOURCES – Sagami; Taisho.

REFERENCES

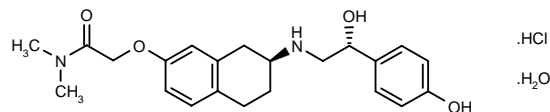
1. Kobori, T. et al. (Taisho Pharmaceutical Co., Ltd.; Sagami Chemical Research Center) *Amino cpds. and angiotensin IV receptor agonists*. WO 9805624.

KUL-1248*

266331

257243 (as anhydrous free base)

(-)-2-[7(*S*)-[2(*R*)-Hydroxy-2-(4-hydroxyphenyl)-ethylamino]-5,6,7,8-tetrahydro-2-naphthyl]-*N,N*-dimethylacetamide hydrochloride monohydrate



C₂₂H₂₈N₂O₄ · HCl · H₂O; Mol wt: 438.9489

ACTION – β_2/β_3 -Adrenoceptor agonist with potential for suppressing colic and facilitating stone discharge in urolithiasis. It inhibited spontaneous motility in pregnant rat uterus (EC₅₀ = 17 nM; β_2 -adrenoceptor-mediated response) and in rat colon (EC₅₀ = 49 nM; β_3 -adrenoceptor-mediated response), with a selectivity ratio as regards effects on spontaneously beating rat atria (β_1 -adrenoceptor-mediated effect) of over 100. It was also able to induce relaxation of rabbit and ferret ureter (EC₅₀ = 0.45 μ M and 75 nM, respectively) and reduced intraureteral pressure *in vivo* in both rabbits and ferrets (ED₃₀ = 0.28 and 0.011 mg/kg i.v., respectively), with minimal cardiovascular side effects.

SOURCE – Kissei.

REFERENCES

1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) *Phenylethanolaminotetra-lincarboxamide derivs*. WO 9738970.

2. Akahane, M. et al. *A novel beta2/beta3-adrenoceptor agonist, KUL-1248: The relaxing effect of ureteral smooth muscle and the selectivity for β -adrenoceptor subtypes*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.44.

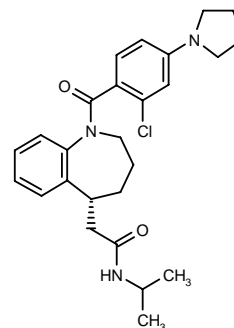
3. Tomiyama, Y. et al. *A novel β_2/β_3 -adrenoceptor agonist, KUL-1248: The effect of the ureteral pressure in anesthetized rabbits and ferrets*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.43.

*Identified compound **257243** Drug Data Report 1998, 020(04): 0326.

OPC-51803

266334

2-[1-[2-Chloro-4-(1-pyrrolidinyl)benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepin-5(*R*)-yl]-*N*-isopropylacetamide



C₂₆H₃₂Cl₂N₃O₂; Mol wt: 454.0108

ACTION – Antidiuretic agent, a selective, nonpeptide vasopressin V_2 receptor agonist ($K_i = 91.9 \pm 10.8$ and 819 ± 39 nM, respectively, for displacement of [3 H]-AVP binding in HeLa cells expressing human V_2 and V_{1a} receptors) shown to concentration-dependently increase V_2 -mediated cAMP production similar to AVP and desmopressin. It was orally effective as an antidiuretic, dose-dependently decreasing urine volume and increasing urinary osmolality in rats with hereditary central diabetes insipidus (0.003-0.3 mg/kg), normal rats (0.03-0.3 mg/kg) and water-loaded conscious dogs (0.03-0.3 mg/kg). Potentially useful for the treatment of central diabetes insipidus and disorders characterized by AVP deficiency.

SOURCE – Otsuka.

REFERENCES

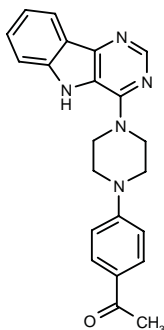
1. Ogawa, H. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzazepine derivs. with vasopressin agonistic activity*. JP 98081668, WO 9722591.
2. Hirano, T. et al. *Antidiuretic effects of OPC-51803, a nonpeptide vasopressin V_2 -receptor agonist, administered orally to Brattleboro rats and normal rats*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 41.22.
3. Nakamura, S. et al. *Antidiuretic effects of OPC-51803, a novel nonpeptide vasopressin V_2 -receptor agonist, administered orally to water-loaded dogs*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 41.23.
4. Nakamura, S. et al. *Characterization of OPC-51803, a novel nonpeptide vasopressin V_2 -receptor agonist*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 19.25.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

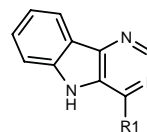
265938

4-[4-(5H-pyrimido[5,4-*b*]indol-4-yl)piperazin-1-yl]acetophenone



C22 H21 N5 O; Mol wt: 371.4419

ACTION – Antiulcer agent with potent activity against *Helicobacter pylori* (MIC = 0.006 μ g/ml or less against *H. pylori* strains NCTC11637 and CPY433 vs. MIC = 0.39 and 6.25 μ g/ml, respectively, for metronidazole). Other compounds from this series of condensed indole derivatives include the following:



Compound	R1	Formula
266516	4-(2-pyrimidinyl)-1-Piz	C ₁₈ H ₁₇ N ₇
266517	4-Ph-1-Piz-CH ₂ CH ₂ O	C ₂₂ H ₂₃ N ₅ O
266518	4-Ph-1,2,3,6-tetrahydro-1-Pyr	C ₂₁ H ₁₈ N ₄

SOURCE – Takeda.

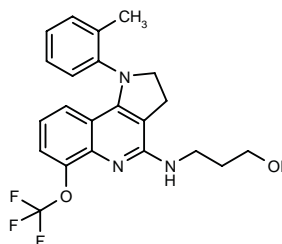
REFERENCES

1. Kamiyama, K. et al. (Takeda Chemical Industries, Ltd.) *Condensed indole derivs., their preparation method and their use*. JP 98175977.

AU-006

266325

3-[1-(2-Methylphenyl)-6-(trifluoromethoxy)-2,3-dihydro-1H-pyrrolo[3,2-*c*]quinolin-4-ylamino]-1-propanol



C22 H22 F3 N3 O2; Mol wt: 417.4288

ACTION – Antiulcer agent able to dose-dependently (30-300 mg/kg) prevent the formation of gastric lesions induced by ethanol and NaOH in rats after oral administration and cysteamine-induced duodenal ulcers in rats following i.p. administration. Its antiulcer effects appeared to be due to decreases in gastric acid secretion. No toxic effects were detected after 3-week subchronic oral administration in rats.

SOURCE – Korea Res. Inst. Chem. Technol., TaeJon (KR).

REFERENCES

1. Cheon, H.G. et al. *Pharmacological studies of a new quinoline derivative, AU-006, with potent anti-ulcer effect*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.19.
2. Kim, H.J. and Cheon, H.G. *Effect of AU-006, a new antiulcer agent, on experimentally induced ulcer and gastric secretion in rat*. Symp Curr Top Pharmacol Toxicol (Oct 13-14, Seoul) 1997, Abst P052.

ACTION – Antidiuretic agent, a selective, nonpeptide vasopressin V_2 receptor agonist ($K_i = 91.9 \pm 10.8$ and 819 ± 39 nM, respectively, for displacement of [3 H]-AVP binding in HeLa cells expressing human V_2 and V_{1a} receptors) shown to concentration-dependently increase V_2 -mediated cAMP production similar to AVP and desmopressin. It was orally effective as an antidiuretic, dose-dependently decreasing urine volume and increasing urinary osmolality in rats with hereditary central diabetes insipidus (0.003-0.3 mg/kg), normal rats (0.03-0.3 mg/kg) and water-loaded conscious dogs (0.03-0.3 mg/kg). Potentially useful for the treatment of central diabetes insipidus and disorders characterized by AVP deficiency.

SOURCE – Otsuka.

REFERENCES

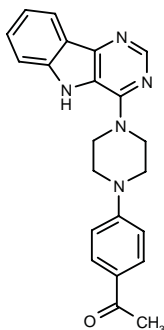
1. Ogawa, H. et al. (Otsuka Pharmaceutical Co., Ltd.) *Benzazepine derivs. with vasopressin agonistic activity*. JP 98081668, WO 9722591.
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

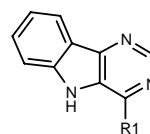
265938

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C22 H21 N5 O; Mol wt: 371.4419

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266517	4-Ph-1-Piz-CH ₂ CH ₂ O	C ₂₂ H ₂₃ N ₅ O
266518	4-Ph-1,2,3,6-tetrahydro-1-Pyr	C ₂₁ H ₁₈ N ₄

SOURCE – Takeda.

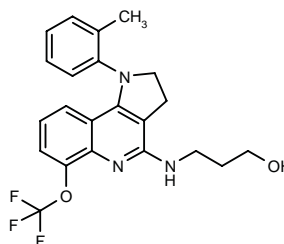
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1. Kamiyama, K. et al. (Takeda Chemical Industries, Ltd.) *Condensed indole derivs., their preparation method and their use*. JP 98175977.

AU-006

266325

3-[1-(2-Methylphenyl)-6-(trifluoromethoxy)-2,3-dihydro-1H-pyrrolo[3,2-*c*]quinolin-4-ylamino]-1-propanol



C22 H22 F3 N3 O2; Mol wt: 417.4288

ACTION – Antiulcer agent able to dose-dependently (30-300 mg/kg) prevent the formation of gastric lesions induced by ethanol and NaOH in rats after oral administration and cysteamine-induced duodenal ulcers in rats following i.p. administration. Its antiulcer effects appeared to be due to decreases in gastric acid secretion. No toxic effects were detected after 3-week subchronic oral administration in rats.

SOURCE – Korea Res. Inst. Chem. Technol., TaeJon (KR).

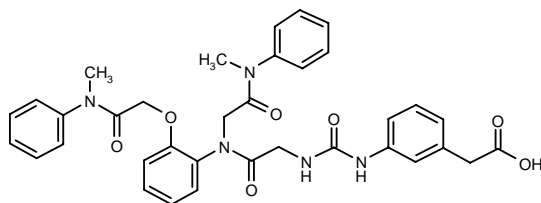
REFERENCES

1. Cheon, H.G. et al. *Pharmacological studies of a new quinoline derivative, AU-006, with potent anti-ulcer effect*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.19.
2. Kim, H.J. and Cheon, H.G. *Effect of AU-006, a new antiulcer agent, on experimentally induced ulcer and gastric secretion in rat*. Symp Curr Top Pharmacol Toxicol (Oct 13-14, Seoul) 1997, Abst P052.

DA-3934

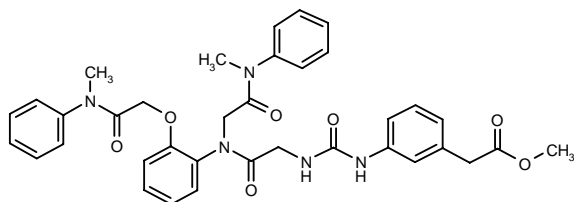
265750

2-[3-[3-[N-[2-(N-Methyl-N-phenylcarbamoylmethoxy)-phenyl]-N-(N-methyl-N-phenylcarbamoylmethyl)-carbamoylmethyl]ureido]phenyl]acetic acid



C35 H35 N5 O7; Mol wt: 637.6895

ACTION – Potent and selective CCK_B/gastrin receptor antagonist giving IC₅₀ values in binding studies of 0.4 nM for the human gastrin receptor and of 877 nM for the human CCK_A receptor. *In vivo*, the compound inhibited pentagastrin-induced gastric acid secretion in anesthetized rats with ED₅₀ values of 5.2 mg/kg intra-duodenally and 12.5 µg/kg i.v. The methyl ester (**265853**) also potently inhibited gastric acid secretion *in vivo* (ED₅₀ = 1.5 mg/kg i.d.).



265853: C36 H37 N5 O7

CCK_B/gastrin receptor antagonists are thought to have therapeutic potential in the treatment of both peptic ulcers and CNS disorders.

SOURCE – Daiichi Pharmaceutical.

REFERENCES

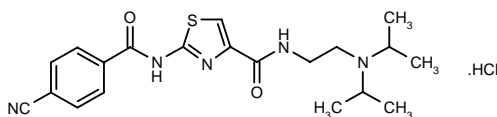
1. Yokohama, S. et al. (Daiichi Pharmaceutical Co., Ltd.) *Aminophenol derivs.* WO 9628416.

2. Takeda, Y. et al. *Synthesis of phenoxyacetic acid derivatives as highly potent antagonists of gastrin/cholecystokinin-B receptors. II.* Chem Pharm Bull 1998, 46(6): 951.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

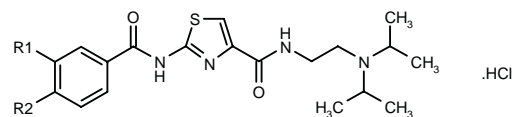
264881

2-(4-Cyanobenzamido)-N-[2-(diisopropylamino)-ethyl]thiazole-4-carboxamide hydrochloride



C20 H25 N5 O2 S . HCl; Mol wt: 435.9774

ACTION – Gastric prokinetic and antiemetic agent proven to increase gastric motility in dogs at 1 mg/kg i.v. No deaths occurred following administration of 500 mg/kg p.o. to mice. Within this series of benzoylaminothiazoles, the following are also included:



Compound	R1	R2	Formula
266029	CN	H	C ₂₀ H ₂₅ N ₅ O ₂ S.HCl
266030	H	Ac	C ₂₁ H ₂₈ N ₄ O ₃ S.HCl
266031	Ac	H	C ₂₁ H ₂₈ N ₄ O ₃ S.HCl

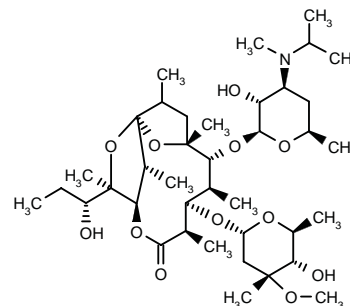
SOURCE – Zeria.

REFERENCES

1. Nagasawa, M. et al. (Zeria Pharmaceutical Co., Ltd.) *Subst. benzoylaminothiazoles derivs. and drugs containing the same.* WO 9817654.

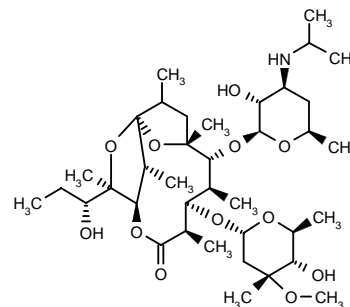
265148

[1*R*,4*R*,5*S*,6*S*,7*R*,8*R*,11*R*,13*R*(1'*R*),14*R*]-5-(2,6-Dideoxy-3-*C*,3-*O*-dimethyl-α-*L*-altropyranosyloxy)-13-(1-hydroxypropyl)-4,6,8,10,13,14-hexamethyl-7-[3,4,6-trideoxy-3-(*N*-isopropyl-*N*-methylamino)-β-*D*-glucopyranosyloxy]-2,12,15-trioxatricyclo[9.2.1.1^{8,11}]-pentadecan-3-one



C39 H69 N O12; Mol wt: 743.9691

ACTION – Gastric prokinetic agent with motilin receptor-agonist activity (pIC₅₀ = 7.85 in a binding assay using [¹²⁵I]-motilin as the ligand). Another exemplified compound is:



265956: C38 H67 N O12

SOURCE – Solvay.

REFERENCES

1. Høltje, D. et al. (Solvay SA) 10,13-15-Trioxatricyclo[9.2.1.1.9.6]-pentadecanon derivs., process for their preparation and medicament containing them. EP 838469, JP 98130297.

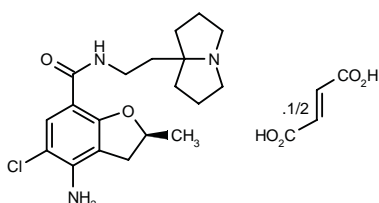
SK-951*

265589

223944 (as free base)

234433 (as racemic)**

(-)-4-Amino-N-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-5-chloro-2(S)-methyl-2,3-dihydrobenzo[b]furan-7-carboxamide hemifumarate



C19 H26 Cl N3 O2 . 1/2C4 H4 O4; Mol wt: 421.9230

M.p. 236 °C (decomp.), $[\alpha]_D^{20} -3.2^\circ$ (c 5.00, MeOH:H2O 1:1).

ACTION – Potent 5-HT₄ receptor agonist (ED₅₀ = 14 nM for relaxation of carbachol-induced tone in rat esophagus) shown to be more potent than the racemate** (ED₅₀ = 30 nM) and the (R)-(+)-enantiomer (ED₅₀ = 32 nM). It showed no affinity for dopamine D₁ or D₂ or 5-HT₁ binding sites (IC₅₀ > 100 μM) and relatively weak affinity for 5-HT₂ and muscarinic M₁ and M₂ receptors (IC₅₀ = 1.3-19 μM), although it does have significant affinity for 5-HT₃ receptors (IC₅₀ = 0.42 μM). Selected as a promising candidate for a selective gastric prokinetic agent.

SOURCE – Sanwa.

REFERENCES

1. Baba, Y. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) Benzo[b]furancarboxamide derivs., process for their preparation and their use as gastrointestinal mobility-enhancing agents. EP 640602, JP 95112985, US 5442077.

2. Kakigami, T. et al. Serotonin 5-HT₄ receptor agonistic activity of the optical isomers of (±)-4-amino-N-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-5-chloro-2,3-dihydro-2-methylbenzo[b]furan-7-carboxamide. Chem Pharm Bull 1998, 46(6): 1039.

*Identified compound 223944 (see 221803) Drug Data Report 1995, 017(08): 0739.

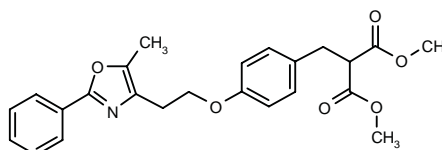
**See SKK-47029 Drug Data Report 1996, 018(06): 0538.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

265286

2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-malonic acid dimethyl diester



C24 H25 N O6; Mol wt: 423.4625

Colorless solid, m.p. 87.9-8.5 °C.

ACTION – Potent antihyperglycemic agent selected from a series of noncyclic 1,3-dicarbonyl compounds as a successor to JTT-501. It displayed potent insulin-sensitizing activity, as demonstrated by its ability to enhance insulin-induced triglyceride accumulation in 3T3-L1 cells (EC₅₀ = 0.059 nM). The compound reduced blood glucose levels in genetically diabetic KKA^y mice with ED₂₅ and ED₅₀ values of 0.011 and 0.17 mg/kg/day in the diet, respectively.

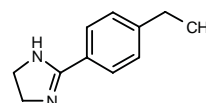
SOURCE – Japan Tobacco.

REFERENCES

1. Shinkai, H. et al. Isoxazolidine-3,5-dione and noncyclic 1,3-dicarbonyl compounds as hypoglycemic agents. J Med Chem 1998, 41(11): 1927.

265430

2-(4-Ethylphenyl)-4,5-dihydro-1H-imidazole



C11 H14 N2; Mol wt: 174.2456

ACTION – Agent for the treatment of diabetes, CNS disorders such as depression, Parkinson's disease and anorexia, cardiovascular disorders such as hypertension, obesity, anemia and cancer with nanomolar affinity for imidazoline I₁ and/or I₂ receptors and devoid of affinity for α₁- and α₂-adrenoceptors. It inhibits adipocyte MAO and is reported to have potent hypoglycemic activity in rats with streptozotocin-induced diabetes.

SOURCE – ADIR.

REFERENCES

1. Payard, M. et al. (ADIR et Cie.) New imidazoline derivs. having activity for the imidazoline receptor. EP 846688, JP 98168065.

REFERENCES

1. Høltje, D. et al. (Solvay SA) 10,13-15-Trioxatricyclo[9.2.1.1.9.6]-pentadecanon derivs., process for their preparation and medicament containing them. EP 838469, JP 98130297.

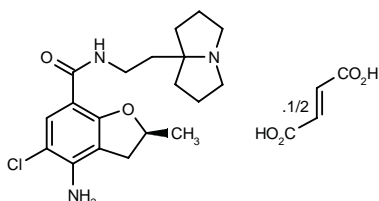
SK-951*

265589

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*Identified compound 223944 (see 221803) Drug Data Report 1995, 017(08): 0739.

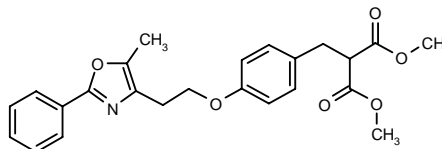
**See SKK-47029 Drug Data Report 1996, 018(06): 0538.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

265286

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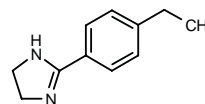
SOURCE – Japan Tobacco.

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1. Shinkai, H. et al. Isoxazolidine-3,5-dione and noncyclic 1,3-dicarbonyl compounds as hypoglycemic agents. J Med Chem 1998, 41(11): 1927.

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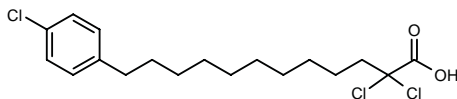
SOURCE – ADIR.

REFERENCES

1. Payard, M. et al. (ADIR et Cie.) New imidazoline derivs. having activity for the imidazoline receptor. EP 846688, JP 98168065.

BM-17.0744**265033**

12-(4-Chlorophenyl)-2,2-dichlorododecanoic acid



C18 H25 Cl3 O2; Mol wt: 379.7525

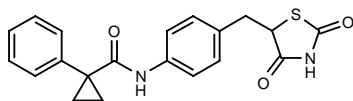
ACTION – Hypoglycemic, insulin-potentiating and hypolipidemic agent from a series of ω -substituted alkyl carboxylic acids with a pharmacological and toxicological profile indicating potential in the treatment of type II diabetes, especially in patients with metabolic syndrome. Blood glucose-lowering activity was observed in diabetic *ob/ob* mice, serum insulin-lowering effects were noted in yellow KK mice, glucose disposal rate was improved in obese *fa/fa* Zucker rats and blood lipid-lowering effects were observed in both diabetic and healthy animals.

SOURCE – Roche.**REFERENCES**

1. Pill, J. et al. ω -Substituted alkyl carboxylic acids: A novel group of compounds with insulin-potentiating, antidiabetic and lipid lowering activity. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 77.

DN-108***256868**

N-[4-(2,4-Dioxothiazolidin-5-ylmethyl)phenyl]-1-phenyl-cyclopropane-1-carboxamide



C20 H18 N2 O3 S; Mol wt: 366.4420

ACTION – Potent, orally active thiazolidinedione anti-diabetic agent that appears to act by sensitizing peripheral tissues for glucose uptake. It was effective in improving hyperglycemia, hypertriglyceridemia and hyperinsulinemia in KKA γ and *db/db* mice given doses of 10-30 mg/kg/day p.o. for 10 days, whereas troglitazone 100 mg/kg/day had no significant effect; it was also much more potent than troglitazone in lowering serum glucose levels in KKA γ mice when administered for 4 days (ED_{25} = 7 and 283 mg/kg/day, respectively). Both compounds increased basal 2-deoxyglucose uptake in L6 muscle cells and similarly inhibited aldose reductase activity (IC_{50} = 3.6 and 3.8 μ M, respectively, for DN-108 and troglitazone).

SOURCE – Torii.**REFERENCES**

1. Taira, S. and Sugimoto, A. (Torii Pharmaceutical Co., Ltd.) Thiazolidine-2,4-dione derivs. WO 9732863.

2. Ueda, N. et al. Pharmacological and pharmacokinetic studies of newly synthesized thiazolidinedione derivative 5-(4-(1-phenyl-1-cyclopropanecarbonylamino)benzyl)-thiazolidine-2,4-dione. *Arzneim-Forsch Drug Res* 1998, 48(6): 651.

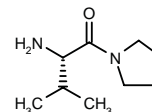
3. Ueda, N. et al. Pharmacological and pharmacokinetic studies of the newly synthesized thiazolidinedione derivative 5-(4-(1-phenyl-1-cyclopropanecarbonylamino)benzyl)thiazolidine-2,4-dione. *Naunyn-Schmied Arch Pharmacol* 1998, 48(6): 651.

*Identified compound **256868** (see **255670**) Drug Data Report 1997, 019(11): 1003.

SDZ-272-070**253941**

1-(L-Valyl)pyrrolidine

(S)-1-(2-Amino-3-methyl-1-oxobutyl)pyrrolidine



C9 H18 N2 O; Mol wt: 170.2542

ACTION – Stable and selective inhibitor of the aminopeptidase dipeptidyl peptidase IV (DPP IV; K_i approx. 0.4 μ mol/l), proven to markedly increase the amount of intact glucagon-like peptide 1 (GLP-1) during an infusion in anesthetized pigs at a dose (300 μ mol/kg by i.v. bolus) producing over 90% inhibition of basal DPP IV activity, and thereby prolong the plasma half-life of intact GLP-1. It potentiated the effect of i.v. GLP-1 on the incremental AUC for glucose and insulin in the nonfasted state, and it also increased the insulin response to a glucose load given during GLP-1 infusion. Similar results were observed in insulin-resistant, glucose-intolerant rats. It thus appears to have potential in the management of non-insulin-dependent diabetes mellitus (NIDDM).

SOURCE – Novartis.**REFERENCES**

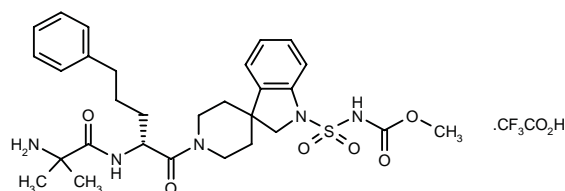
1. Balkan, B. et al. Improved insulin secretion and oral glucose tolerance after in vivo inhibition of DPP-IV in obese Zucker rats. *Diabetologia* 1997, 40(Suppl. 1): Abst 511.

2. Deacon, C.F. et al. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. *Diabetes* 1998, 47(5): 764.

3. Li, X. et al. Improved insulin secretion and oral glucose tolerance after in vivo inhibition of DPP-IV in insulin resistant rats. *Diabetes* 1997, 46(Suppl. 1): Abst 0910.

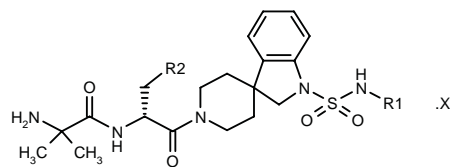
TREATMENT OF GROWTH HORMONE SECRETION DISORDERS**267268**

N-[1'-[2(R)-(2-Amino-2-methylpropionamido)-5-phenylpentanoyl]spiro[indole-2(3H),4'-piperidin]-1-ylsulfonfyl]-carbamic acid methyl ester trifluoroacetate



C29 H39 N5 O6 S . C2 H F3 O2; Mol wt: 699.7440

ACTION – Growth hormone (GH) secretagogue able to stimulate the release of natural or endogenous GH, claimed for the treatment of various conditions, particularly osteoporosis, but also catabolic illness, immune deficiency, hip fracture, musculoskeletal impairment in the elderly, GH deficiency in adults or children, obesity, and cachexia and protein loss due to chronic illness such as AIDS or cancer. Within this series of spiro compounds, the following are also included:



Compound	R1	R2	X	Formula
267269	CO2Me	3-indolyl	CF3CO2H	C ₂₉ H ₃₆ N ₆ O ₆ S .C ₂ H ₅ F ₃ O ₂
267270	Ac	CH2CH2Ph	HCl	C ₂₉ H ₃₆ N ₆ O ₅ S.HCl
267271	i-PrCO	CH2CH2Ph	HCl	C ₃₁ H ₄₃ N ₆ O ₅ S.HCl
267272	H	CH2CH2Ph	HCl	C ₂₇ H ₃₇ N ₆ O ₄ S.HCl

SOURCE – Merck & Co.

REFERENCES

1. Guo, L. et al. (Merck & Co., Inc.) Piperidines and hexahydro-1H-azepines spiro substd. at the 4-position promote release. US 5783582, WO 9602530.

TREATMENT OF MALE SEXUAL DYSFUNCTION

INVICORP™

252788

An injectable formulation of vasoactive intestinal polypeptide (VIP) in combination with the adrenergic drug phentolamine mesilate

ACTION – Autoinjectable formulation of vasoactive intestinal peptide (VIP) and phentolamine mesilate for the treatment of male erectile dysfunction. It has been approved in Denmark.

SOURCE – Senetek.

REFERENCES

1. Dean, J. and Budhram, R.K. A retrospective long term safety study of Invicorp in the management of male erectile dysfunction (MED). Int J Impot Res 1998, 10(Suppl. 3): Abst 183.

2. Dinsmore, W.W. et al. Vasoactive intestinal polypeptide and phentolamine mesylate by autoinjector in pharmaco resistant erectile dysfunction. 2nd Meet Eur Soc Impotence Res (Oct 1-4, Madrid) 1997, Abst 114.

3. Hackett, G. et al. A 12 month multicentre placebo controlled study of Invicorp in the treatment of non-psychogenic erectile dysfunction. Int J Impot Res 1998, 10(Suppl. 3): Abst 166.

4. Hackett, G. et al. A study to evaluate the use of Invicorp (a combination of VIP with phentolamine) to diagnose and treat ED using a problem orientated management procedure. 2nd Meet Eur Soc Impotence Res (Oct 1-4, Madrid) 1997, Abst 124.

5. Hackett, G. et al. The results of a 6 month, multi-centre placebo controlled study of Invicorp in the treatment of non-psychogenic erectile dysfunction. J Urol 1998, 159(5, Suppl.): Abst 918.

6. Kim, N.N. et al. Potentiation of VIP-induced relaxation by phentolamine in corpus cavernosum. Int J Impot Res 1998, 10(Suppl. 3): Abst 327.

7. Metz, P. and Gerstenberg, T.C. An open label study of the long term efficacy and safety of Invicorp (a combination of VIP and phentolamine) for the treatment of erectile dysfunction. 2nd Meet Eur Soc Impotence Res (Oct 1-4, Madrid) 1997, Abst 3.

8. Otteson, B. et al. A study to evaluate the effects of a combination of VIP and phentolamine on sperm analysis. Int J Impot Res 1998, 10(Suppl. 3): Abst 185.

9. Sandhu, D. et al. An investigation of the dose-response relationships of vasoactive intestinal polypeptide (VIP) and phentolamine when given by intracavernosal injection to patients with erectile dysfunction (ED). Int J Impot Res 1998, 10(Suppl. 3): Abst 182.

10. A open label study of the long term efficacy and safety of Invicorp(TM) (a combination of VIP and phentolamine) for the treatment of erectile dysfunction. Senetek plc Web Site 1998, July 16.

11. A pilot study of the role of intracavernous injection of vasoactive intestinal peptide (VIP) and phentolamine mesylate in the treatment of erectile dysfunction. Senetek plc Web Site 1998, July 16.

12. A study to evaluate the use of Invicorp (a combination of vasoactive intestinal polypeptide - VIP with phetolamine) to diagnose and treat ED using a problem orientated management procedure. Senetek plc Web Site 1998, July 16.

13. Additional PLAs filed for Invicorp. Daily Essentials 1997, Sept 22.

14. Erectile dysfunction (ED) attracts competition. Senetek plc Web Site 1998, July 16.

15. INVICORP shows 70% efficacy in ED study. Daily Essentials 1998, March 13.

16. Invicorp(TM) - A combination of vasoactive intestinal polypeptide (VIP) and phentolamine mesylate by autoinjector - In pharmaco resistant erectile dysfunction. Senetek plc Web Site 1998, July 16.

17. Promising results reported for of Senetek's INVICORP for male erectile dysfunction. Daily Essentials 1998, Dec 30.

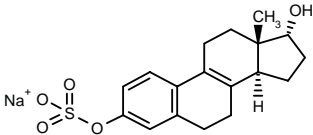
18. Senetek's ED treatment shows 83% response rate. Daily Essentials 1998, May 15.

19. Vasoactive intestinal peptide and phentolamine: Pharmacology, efficacy, safety and novel auto injector system. Senetek plc Web Site 1998, July 16.

TREATMENT OF GYNECOLOGICAL DISORDERS

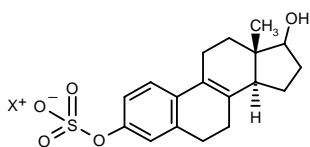
264853

3-(Sulfooxy)estra-1,3,5(10),8-tetraen-17α-ol sodium salt



C18 H21 Na O5 S; Mol wt: 372.4149

ACTION – A metabolite of Δ^{8,9}-dehydroestrone with more potent estrogenic properties than parent compound, as demonstrated *in vivo* by measuring uterine growth in immature female mice. Compound was also found to exhibit antioxidant properties, as demonstrated by inhibition of LDL oxidation induced by exposure to Cu²⁺ ions (IC₅₀ = 0.19 μM) or porcine aortic endothelial cells (IC₅₀ = 0.26 μM vs. 0.56 μM for estrone). Claimed for use in estrogen replacement therapy, for relieving symptoms related to estrogen deficiency, for preventing bone loss and for the treatment of atherosclerosis. By virtue of its antioxidant properties, compound may also be useful for the treatment of any disorder involving the production of free radicals, including cancer, CNS disorders and Alzheimer's disease. Other metabolites of Δ^{8,9}-dehydroestrone are:



Compound	X ⁺	Isomer	Formula
266257	NH(Et)3 ⁺	17α	C ₂₄ H ₃₇ NO ₅ S
266258	Na ⁺	17β	C ₁₈ H ₂₁ NaO ₅ S
266259	NH(Et)3 ⁺	17β	C ₂₄ H ₃₇ NO ₅ S

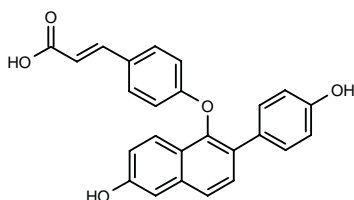
SOURCE – American Home Products.

REFERENCES

- Adelman, S.J. et al. (American Home Products Corp.) 8(9)-Dehydroestradiol derivs. WO 9816544.

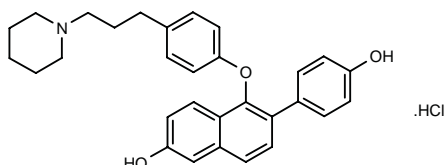
265137

3-[4-[6-Hydroxy-2-(4-hydroxyphenyl)naphthalen-1-yloxy]-phenyl]-2-propenoic acid



C25 H18 O5; Mol wt: 398.4122

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancer. In ovariectomized rats, compound produced a significant decrease in serum cholesterol levels (34.7%) at 1 mg/kg/day p.o. x 4 days, with no stimulatory effect on the uterus or on eosinophil infiltration into the uterus, contrary to 17α-ethinylestradiol at 0.1 mg/kg/day p.o. x 4 days. In addition, it inhibited the proliferation of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 400 nM. Another specifically claimed compound from this series of 1-aryloxy-2-arylnaphthyl derivatives is:



265856: C30 H31 N O3.HCl

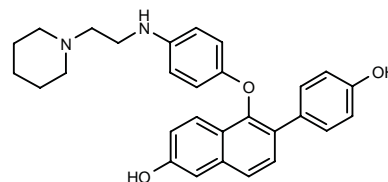
SOURCE – Lilly.

REFERENCES

- Hauser, K.L. and Palkowitz, A.D. (Eli Lilly and Company) 1-Aryloxy-2-arylnaphthyl cpds., intermediates, compsns., and methods. EP 835867, JP 98204028.

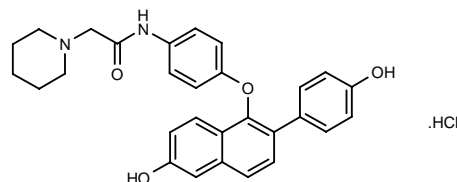
265138

6-(4-Hydroxyphenyl)-5-[4-[2-(1-piperidinyl)ethylamino]-phenoxy]-2-naphthol



C29 H30 N2 O3; Mol wt: 454.5670

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancer. In ovariectomized rats, compound produced a 75.3% decrease in serum cholesterol levels at 1 mg/kg/day p.o. x 4 days compared to 75.9% for 17α-ethinylestradiol at 0.1 mg/kg/day p.o. x 4 days, with much lower stimulatory effect on the uterus compared to 17α-ethinylestradiol and no stimulatory effect on eosinophil infiltration into the uterus. Another specifically claimed compound is:



265857: C29 H28 N2 O4.HCl

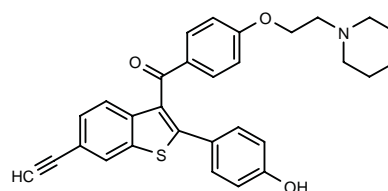
SOURCE – Lilly.

REFERENCES

- Hauser, K.L. and Palkowitz, A.D. (Eli Lilly and Company) 2-Aryl-3-aminoaryl-oxynaphthyl cpds., intermediates, compsns. and methods. EP 835868, JP 98231292.

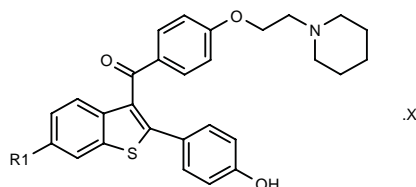
265139

1-[6-Ethynyl-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-1-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone



C30 H27 N O3 S; Mol wt: 481.6133

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, hyperlipidemia and estrogen-dependent cancers such as breast and uterine cancer. In ovariectomized rats, it significantly decreased cholesterol levels at 0.1-10 mg/kg/day p.o. x 4 days, with little stimulatory effect on the uterus and no stimulatory effect on eosinophil infiltration into the uterus, contrary to the effects observed with 17α-ethinylestradiol. It was also found to inhibit the proliferation of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 20 nM. Other compounds from this series of benzo[b]thiophenes include the following:



Compound	R1	X	Formula
266007	CO ₂ Me	HCl	C ₃₀ H ₂₉ NO ₅ S.HCl
266008	CO ₂ Bu		C ₃₃ H ₃₅ NO ₅ S
266009	i-BuOCO		C ₃₃ H ₃₅ NO ₅ S
266010	CO ₂ H	HCl	C ₂₉ H ₂₇ NO ₅ S.HCl
266011	Ac		C ₃₀ H ₂₉ NO ₄ S

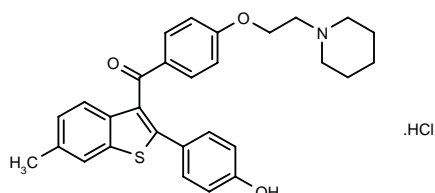
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly and Company) *Benzo[b]thiophene cpds., intermediates, formulations, and methods*. EP 835871, JP 98130258.

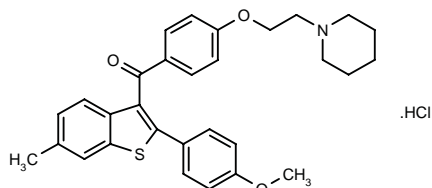
265140

1-[2-[4-Hydroxyphenyl]benzo[*b*]thien-3-yl]-1-[4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride



C₂₉ H₂₉ N O₃ S . HCl; Mol wt: 508.0790

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancer. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 1 mg/kg/day p.o. x 4 days, with lower stimulatory effect on the uterus compared to 17 α -ethinylestradiol at 0.1 mg/kg/day p.o. x 4 days and no stimulatory effect on eosinophil infiltration into the uterus. In addition, it inhibited the growth of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 100 nM. Another specifically claimed compound from this series of benzo[*b*]thiophenes is:



265855: C₃₀ H₃₁ N O₃ S.HCl

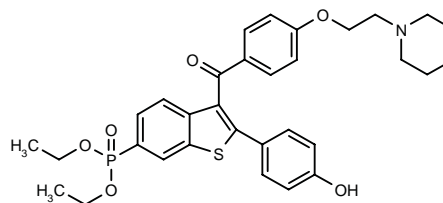
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly and Company) *Benzo[b]thiophene cpds., intermediates, formulations, and methods*. EP 835872, JP 98130259.

265141

2-(4-Hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]benzo[*b*]thiophene-6-phosphonic acid diethyl ester



C₃₂ H₃₆ N O₆ P S; Mol wt: 593.6774

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancer. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 10 mg/kg/day p.o. x 4 days, with little stimulatory effect on the uterus compared to 17 α -ethinylestradiol at 0.1 mg/kg/day p.o. x 4 days and no stimulatory effect on eosinophil infiltration into the uterus. In addition, it inhibited the growth of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 100 nM.

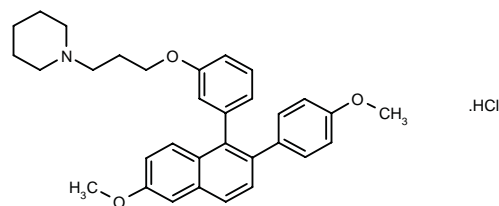
SOURCE – Lilly.

REFERENCES

1. Bryant, H.U. et al. (Eli Lilly and Company) *Benzo(b)thiophene cpds., intermediates, formulations, and methods*. EP 835878, JP 98147583.

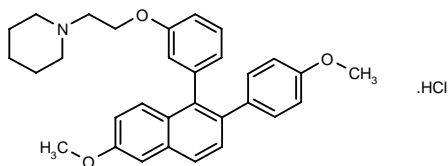
265144

1-[3-[3-[6-Methoxy-2-(4-methoxyphenyl)naphthalen-1-yl]phenoxy]propyl]piperidine hydrochloride



C₃₂ H₃₅ N O₃ . HCl; Mol wt: 518.0934

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, hyperlipidemia and estrogen-dependent cancer, as well as uterine fibroid disease, endometriosis and aortic smooth muscle cell proliferation. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 0.1 mg/kg p.o., while showing much lower increases in uterine weight and uterus eosinophil infiltration than 17 α -ethinylestradiol at the same dose. Another compound from this series of naphthyl derivatives is:



265889: C₃₁ H₃₃ N O₃.HCl

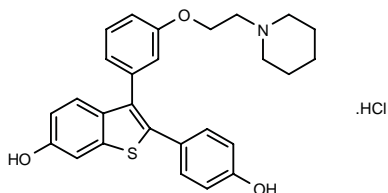
SOURCE – Lilly.

REFERENCES

1. Cullinan, G.J. and Muehl, B.S. (Eli Lilly and Company) *Naphthyl cpds., compsns., and methods*. EP 838459, JP 98130212.

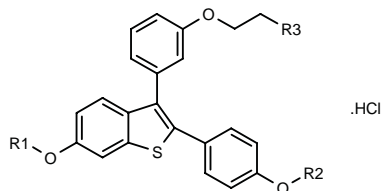
265145

2-(4-Hydroxyphenyl)-3-[3-[2-(1-piperidyl)ethoxy]-phenyl]benzo[b]thiophen-6-ol hydrochloride



C₂₇ H₂₇ N O₃ S . HCl; Mol wt: 482.0412

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia and estrogen-dependent cancer, as well as uterine fibroid disease, endometriosis and restenosis. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 0.1 and 1 mg/kg/day p.o. x 4 days, with little stimulatory effect on the uterus, contrary to 17 α -ethinylestradiol, and no stimulatory effect on eosinophil infiltration into the uterus. In addition, it inhibited the proliferation of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 8 nM. In competition binding studies using [³H]-17 β -estradiol, compound exhibited a relative binding affinity (RBA, IC₅₀ 17 β -estradiol/IC₅₀ test compound) of 0.15 for estrogen receptors from MCF-7 cell preparations. A representative compound from a series of substituted 2,3-aryl-benzo[b]thiophene derivatives, wherein the following are also included:



Compound	R1=R2	R3	Formula
265884	Me	1-Pip	C ₂₉ H ₃₁ NO ₃ S.HCl
265885	Me	1-Pip-CH ₂	C ₃₀ H ₃₃ NO ₃ S.HCl
265886	Me	1-Pip-CH ₂ CH ₂	C ₃₁ H ₃₅ NO ₃ S.HCl
265887	H	1-Pip-CH ₂	C ₂₈ H ₂₉ NO ₃ S.HCl
265888	H	1-Pip-CH ₂ CH ₂	C ₂₉ H ₃₁ NO ₃ S.HCl

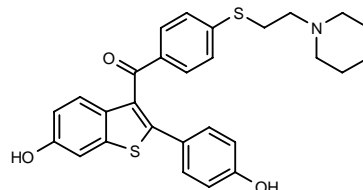
SOURCE – Lilly.

REFERENCES

1. Cullinan, G.J. and Muehl, B.S. (Eli Lilly and Company) *Substd. 2,3-aryl-benzothiophene cpds. having estrogenic activity*. EP 838461, JP 98130260.

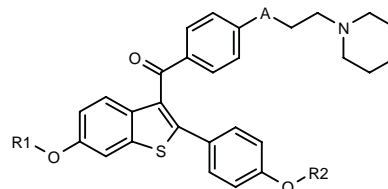
265146

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophen-3-yl]-1-[4-[2-(1-piperidyl)ethylsulfanyl]phenyl]metanone



C₂₈ H₂₇ N O₃ S₂; Mol wt: 489.6573

ACTION – Agent for the treatment of postmenopausal syndrome conditions such as osteoporosis, cardiovascular disorders such as hyperlipidemia, estrogen-dependent cancer and restenosis. In ovariectomized rats, compound was shown to significantly decrease serum cholesterol levels at 1 and 10 mg/kg/day p.o. x 4 days, with much lower stimulatory effect on the uterus compared to 17 α -ethinylestradiol at 0.1 mg/kg/day p.o. x 4 days and no stimulatory effect on eosinophil infiltration into the uterus. In addition, it inhibited the proliferation of breast adenocarcinoma MCF-7 cells with an IC₅₀ value of 0.9 nM. In competition binding studies using [³H]-17 β -estradiol, compound exhibited a relative binding affinity (RBA, IC₅₀ 17 β -estradiol/IC₅₀ test compound) of 0.15 for estrogen receptors from MCF-7 cell preparations. Other specifically claimed compounds from this series of benzo[b]-thiophenes include the following:

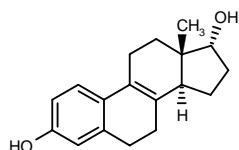


Compound	R1=R2	A	Formula
265880	H	-NH-	C ₂₈ H ₂₈ N ₂ O ₃ S
265881	H	-N(Me)-	C ₂₉ H ₃₀ N ₂ O ₃ S
265882	Me	SO ₂	C ₃₀ H ₃₁ NO ₅ S ₂
265883	H	SO ₂	C ₂₈ H ₂₇ NO ₅ S ₂

SOURCE – Lilly.

REFERENCES

1. Marron, K.S. et al. (Eli Lilly and Company) *Substd. benzo(b)thiophene cpds. having activity as selective estrogen receptor modulators*. EP 838464, JP 98204082.

J-811**264747**Estra-1,3,5(10),8-tetraene-3,17 α -diol

C18 H22 O2; Mol wt: 270.3698

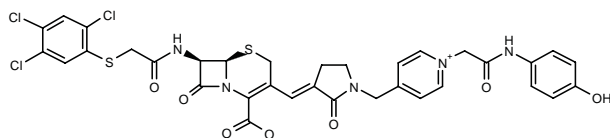
ACTION – Synthetic, nonfeminizing, radical-scavenging estrogen (“scavestrogen”) considered a promising candidate for gender-independent estrogen replacement therapy. It showed marked antiatherosclerotic and significant hypolipidemic effects in cholesterol-fed male rabbits and evidence of CNS-selective estrogen-like activity in ovariectomized rats; in the latter, it demonstrated anxiolytic effects and improvement in cognition upon chronic administration at doses with little effect on the genital tract. In addition, it was equipotent to 17 β -estradiol in neurotrophic/neuroprotective and radical-scavenging effects in rat brain, whereas it had significantly lower affinity for the estrogen receptor ER α and little activity in a transactivation assay compared to 17 β -estradiol, and uterotrophic effects were at least 100 times lower than those of 17 β -estradiol in rats.

SOURCE – Jenapharm.**REFERENCES**

1. Hubler, D. et al. *Effects of scavestrogens on progression of atherosclerosis in cholesterol-fed male rabbits*. 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P2-430.
2. Patchev, V. et al. *Non-feminizing radical scavenging estrogens: Evidence for selective neurotropic action in vivo and implications in neuroprotection*. 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, 195.

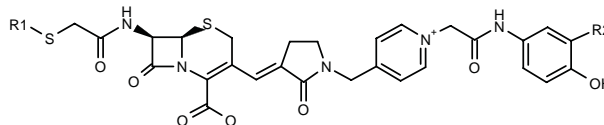
ANTIINFECTIVE THERAPY **β -LACTAM ANTIBIOTICS****265158**

(6*R*,7*R*)-3-[1-[1-[*N*-(4-Hydroxyphenyl)carbamoylmethyl]-pyridinium-4-ylmethyl]-2-oxopyrrolidin-3(*E*)-ylidene-methyl]-7-[2-(2,4,5-trichlorophenylsulfanyl)acetamido]-3-cephem-4-carboxylate

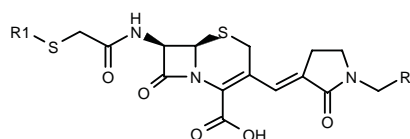


C34 H28 Cl3 N5 O7 S2; Mol wt: 789.1142

ACTION – Cephalosporin antibiotic active *in vitro* against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* strains such as 6538 (MIC = 0.06 μ g/ml or less) and 270A (MIC = 1 μ g/ml). Other exemplified vinylpyrrolidinone cephalosporin derivatives include the following:



Compound	R1	R2	Formula
265859	2-benzothiazolyl	H	C ₃₅ H ₃₀ N ₆ O ₇ S ₃
265861	4-Pyr	H	C ₃₃ H ₃₀ N ₆ O ₇ S ₂
265862	2-Naph	F	C ₃₈ H ₃₂ FN ₅ O ₇ S ₂



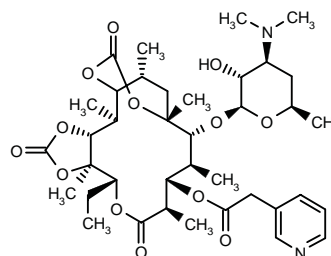
Compound	R1	R2	Formula
265860	2-benzothiazolyl	cyclopropyl	C ₂₈ H ₂₄ N ₆ O ₅ S ₃
265863	2,4,5-(Cl)3-Ph	3-OH-Ph	C ₂₇ H ₂₂ Cl ₃ N ₅ O ₆ S ₂

SOURCE – Roche.**REFERENCES**

1. Angehrn, P. et al. (F. Hoffmann-La Roche AG) *Vinylpyrrolidinon cephalosporin derivs*. EP 841339, JP 98139783.

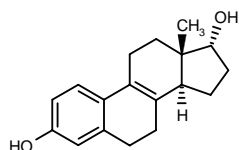
MISCELLANEOUS ANTIBIOTICS**264392**

3-Des(hexopyranosyloxy)-9-deoxy-9-hydroxy-3-[2-(3-pyridyl)acetoxy]erythromycin A 6-*O*,9-*O*:11-*O*,12-*O*-bis-(cyclic carbonate)



C38 H56 N2 O13; Mol wt: 748.8614

ACTION – Antibacterial agent, an erythromycin A derivative with potent and broad-spectrum activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P-JC, *S. aureus* B1, *Staphylococcus epidermidis* IID 866, *Enterococcus faecalis* CSJ 1212, *Haemophilus influenzae* ATCC 33533 and *H. influenzae* ATCC 43095 (MIC = 0.10, 0.20, 0.10, 0.10, 0.78 and 0.78 μ g/ml, respectively), being more potent than azithromycin (MIC = 0.39, > 100, 0.20, 1.56, 1.56 and 1.56 μ g/ml, respectively).

J-811**264747**Estra-1,3,5(10),8-tetraene-3,17 α -diol

C18 H22 O2; Mol wt: 270.3698

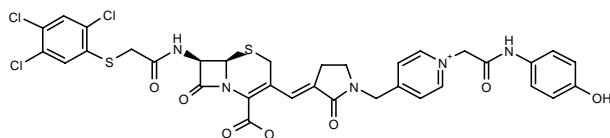
ACTION – Synthetic, nonfeminizing, radical-scavenging estrogen (“scavestrogen”) considered a promising candidate for gender-independent estrogen replacement therapy. It showed marked antiatherosclerotic and significant hypolipidemic effects in cholesterol-fed male rabbits and evidence of CNS-selective estrogen-like activity in ovariectomized rats; in the latter, it demonstrated anxiolytic effects and improvement in cognition upon chronic administration at doses with little effect on the genital tract. In addition, it was equipotent to 17 β -estradiol in neurotrophic/neuroprotective and radical-scavenging effects in rat brain, whereas it had significantly lower affinity for the estrogen receptor ER α and little activity in a transactivation assay compared to 17 β -estradiol, and uterotrophic effects were at least 100 times lower than those of 17 β -estradiol in rats.

SOURCE – Jenapharm.**REFERENCES**

1. Hubler, D. et al. *Effects of scavestrogens on progression of atherosclerosis in cholesterol-fed male rabbits*. 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P2-430.
2. Patchev, V. et al. *Non-feminizing radical scavenging estrogens: Evidence for selective neurotropic action in vivo and implications in neuroprotection*. 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, 195.

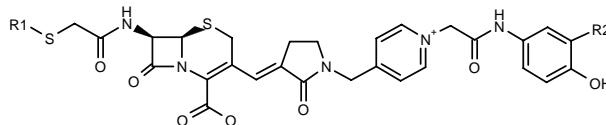
ANTIINFECTIVE THERAPY **β -LACTAM ANTIBIOTICS****265158**

(6*R*,7*R*)-3-[1-[1-[*N*-(4-Hydroxyphenyl)carbamoylmethyl]-pyridinium-4-ylmethyl]-2-oxopyrrolidin-3(*E*)-ylidene-methyl]-7-[2-(2,4,5-trichlorophenylsulfanyl)acetamido]-3-cephem-4-carboxylate

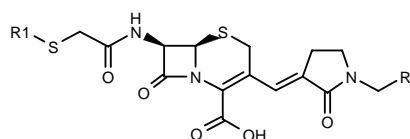


C34 H28 Cl3 N5 O7 S2; Mol wt: 789.1142

ACTION – Cephalosporin antibiotic active *in vitro* against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* strains such as 6538 (MIC = 0.06 μ g/ml or less) and 270A (MIC = 1 μ g/ml). Other exemplified vinylpyrrolidinone cephalosporin derivatives include the following:



Compound	R1	R2	Formula
265859	2-benzothiazolyl	H	C ₃₅ H ₃₀ N ₆ O ₇ S ₃
265861	4-Pyr	H	C ₃₃ H ₃₀ N ₆ O ₇ S ₂
265862	2-Naph	F	C ₃₈ H ₃₂ FN ₅ O ₇ S ₂



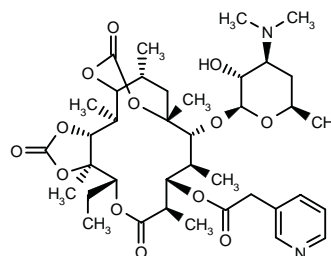
Compound	R1	R2	Formula
265860	2-benzothiazolyl	cyclopropyl	C ₂₈ H ₂₄ N ₆ O ₅ S ₃
265863	2,4,5-(Cl)3-Ph	3-OH-Ph	C ₂₇ H ₂₂ Cl ₃ N ₅ O ₆ S ₂

SOURCE – Roche.**REFERENCES**

1. Angehrn, P. et al. (F. Hoffmann-La Roche AG) *Vinylpyrrolidinon cephalosporin derivs*. EP 841339, JP 98139783.

MISCELLANEOUS ANTIBIOTICS**264392**

3-Des(hexopyranosyloxy)-9-deoxo-9-hydroxy-3-[2-(3-pyridyl)acetoxy]erythromycin A 6-*O*,9-*O*:11-*O*,12-*O*-bis-(cyclic carbonate)



C38 H56 N2 O13; Mol wt: 748.8614

ACTION – Antibacterial agent, an erythromycin A derivative with potent and broad-spectrum activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P-JC, *S. aureus* B1, *Staphylococcus epidermidis* IID 866, *Enterococcus faecalis* CSJ 1212, *Haemophilus influenzae* ATCC 33533 and *H. influenzae* ATCC 43095 (MIC = 0.10, 0.20, 0.10, 0.10, 0.78 and 0.78 μ g/ml, respectively), being more potent than azithromycin (MIC = 0.39, > 100, 0.20, 1.56, 1.56 and 1.56 μ g/ml, respectively).

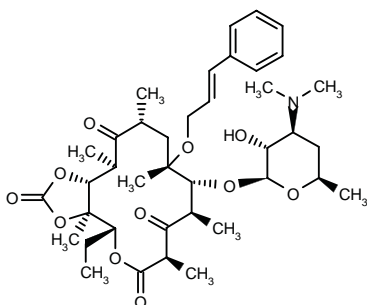
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs.* WO 9813373.

265128

3-Des(hexopyranosyloxy)-3-oxo-6-*O*-[3-phenyl-2(*E*)-propenyl]erythromycin A 11-*O*,12-*O*-cyclic carbonate



C39 H57 N O11; Mol wt: 715.8753

ACTION – Antibacterial agent, an erythromycin A derivative with potent and broad-spectrum activity. *In vitro*, it was active against *Staphylococcus aureus* 209P-JC, *S. aureus* Smith, *Staphylococcus epidermidis* IID 866, *Enterococcus faecalis* CSJ 1212, *Streptococcus pneumoniae* IID 553 and *S. pneumoniae* BM221 (MIC = 0.05, 0.10, 0.05, 0.05, 0.20 and 50 µg/ml, respectively), being generally more potent than azithromycin (MIC = 0.39, 0.39, 0.20, 1.56, 0.20 and > 100 µg/ml, respectively).

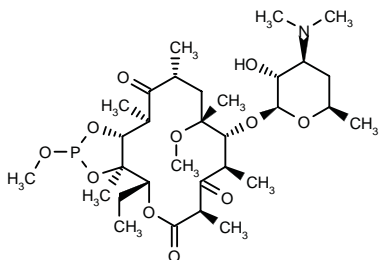
SOURCE – Taisho.

REFERENCES

1. Asaka, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Erythromycin A derivs.* WO 9813373.

266091

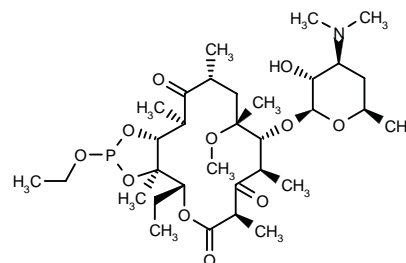
3-Des(cladinosyloxy)-6-*O*-methyl-3-oxoerythromycin A 11-*O*,12-*O*-cyclic phosphite methyl ester



C31 H54 N O11 P; Mol wt: 647.7376

ACTION – Antibacterial agent, a derivative of erythromycin whose activity was tested against a broad range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* ATCC 6538P (MIC = 25 µg/ml), *Staphylococcus epidermidis* 3519 (MIC = 25 µg/ml), *Streptococcus pneumoniae* GYR 1171 (MIC = 8 µg/ml), *Streptococcus pyogenes* EES61 (MIC = 12.5 µg/ml), *Enterococcus faecium* ATCC 8043 (MIC = 25 µg/ml) and *Escherichia coli* SS (MIC = 50 µg/ml); the respective MIC

values for erythromycin A were 0.2, 0.39, 0.06, 0.05, 0.05 and 0.78 µg/ml. Another compound from this series of 11,12-cyclic phosphite or phosphate derivatives of erythromycin is:



266138: C32 H56 N O11 P

SOURCE – Abbott.

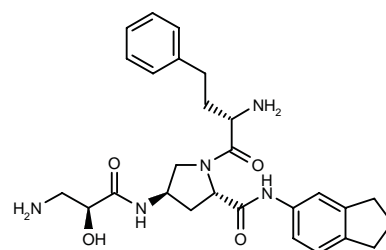
REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) *11,12-Cyclic phosphite or phosphate derivs. of erythromycin and related macrolides.* US 5780604.

MISCELLANEOUS ANTIBACTERIAL DRUGS

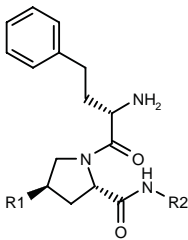
264869

4(*R*)-[3-Amino-2(*S*)-hydroxypropionamido]-1-[2(*S*)-amino-4-phenylbutyryl]-*N*-(5-indanyl)pyrrolidine-2(*S*)-carboxamide

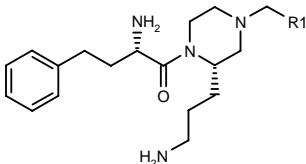


C27 H35 N5 O4; Mol wt: 493.6045

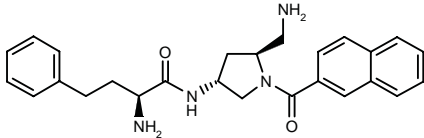
ACTION – Agent for the treatment of bacterial infections that acts by increasing the sensitivity of resistant strains to antimicrobials; a combination of compound and levofloxacin each at a concentration of 2.5 µg/ml produced complete inhibition of the growth of multiple drug-resistant *Pseudomonas aeruginosa* PAM1001. When tested in combination with known antibacterial agents at 10 µg/ml against wild-type *P. aeruginosa* PAM1020, compound was found to potentially increase the effect of levofloxacin (MIC = 0.25 and 0.03 µg/ml in the absence or presence of compound, respectively), rifampicin (MIC = 8 and 0.002 µg/ml, respectively), novobiocin (MIC = 512 and 0.5 µg/ml, respectively), vancomycin (MIC > 256 and 8 µg/ml, respectively) and clarithromycin (MIC = 128 and 0.25 µg/ml, respectively). Other related compounds include the following:



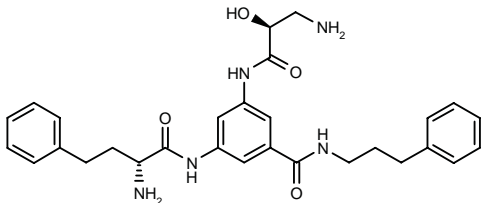
Compound	R1	R2	Formula
266107	NH2	2-Naph	C ₂₅ H ₂₈ N ₄ O ₂
266108	NHCOCH2NH2	2-Naph	C ₂₇ H ₃₁ N ₅ O ₃
266109	NHCOCH2NH2	5-indanyl	C ₂₆ H ₃₃ N ₅ O ₃
266110	H-L-Orn-NH	5-indanyl	C ₂₉ H ₄₀ N ₆ O ₃



Compound	R1	Formula
266113	2-Naph	C ₂₈ H ₃₆ N ₄ O
266114	CH2CH2Ph	C ₂₈ H ₃₈ N ₄ O



266111: C26 H30 N4 O2



266112: C29 H35 N5 O4

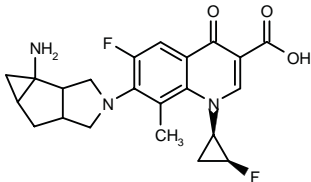
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Ohta, T. et al. (Daiichi Pharmaceutical Co., Ltd.) *Novel remedies for infectious diseases*. WO 9817625.

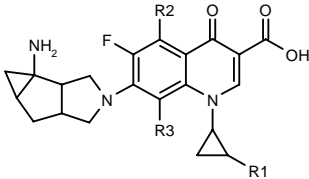
265116

7-(1-Amino-4-azatricyclo[6.1.0.0^{2,6}]nonan-4-yl)-6-fluoro-1-[2(*S*)-fluoro-1(*R*)-cyclopropyl]-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

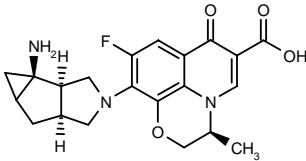


C22 H23 F2 N3 O3; Mol wt: 415.4377

ACTION – Antibacterial agent with potent *in vitro* activity against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 209P (MIC = 0.003 µg/ml or less), *Streptococcus pneumoniae* J24 (MIC = 0.003 µg/ml or less), *Streptococcus pyogenes* G-36 (MIC = 0.003 µg/ml or less), *Pseudomonas aeruginosa* 32121 (MIC = 0.025 µg/ml) and *Escherichia coli* NIHJ (MIC = 0.003 µg/ml or less). Other compounds from this series of tricyclic amines include the following:



Compound	R1	R2	R3	Isomer	Formula
265962	H	NH2	F		C ₂₁ H ₂₂ F ₂ N ₄ O ₃
265964	F	H	OMe	1R,2S	C ₂₂ H ₂₃ F ₂ N ₃ O ₄
265965	F	NH2	Me	1R,2S	C ₂₂ H ₂₄ F ₂ N ₄ O ₃



265963: C21 H22 F2 N3 O4

SOURCE – Daiichi Pharmaceutical.

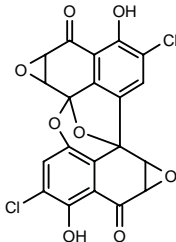
REFERENCES

1. Takemura, M. et al. (Daiichi Pharmaceutical Co., Ltd.) *Tricyclic amine derivs*. WO 9818783.

F-12517

265275

5,12-Dichloro-1,2:7a,13b:8,9-triepoxy-4,11-dihydroxy-1,2,3,7a,8,9,10,13b-octahydrodinaphtho[1,8-*bc*:1',8'-*ef*]oxepine-3,10-dione



C20 H8 Cl2 O8; Mol wt: 447.1812

ACTION – Antibacterial agent isolated from *Vibrissea* SANK18796 (FERM BP-5685), active *in vitro* against Gram-positive bacteria such as *Staphylococcus aureus* 209P (MIC = 0.8 µg/ml) and methicillin-resistant strains of *S. aureus* (MIC = 3.1 µg/ml).

SOURCE – Sankyo.

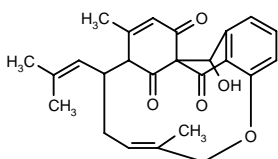
REFERENCES

1. Shimada, A. and Hosoya, T. (Sankyo Co., Ltd.) *Novel cpd. F-12517*. JP 98114778.

ANTIFUNGAL AGENTS

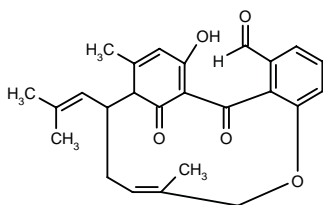
264355

19-Hydroxy-4,17-dimethyl-1-(3-methyl-2-butenyl)-6-oxa-tetracyclo[12.3.1.11^{11,14}.0^{7,12}]nonadeca-3,7,9,11,16-pentaene-13,15,18-trione



C25 H26 O5; Mol wt: 406.4754

ACTION – Chymase inhibitor (IC_{50} = 0.5 μ M against human enzyme) isolated from *Stachybotrys cylindrospora* RF-5900 (FERM P-15742). Compound possesses antifungal activity, giving a MIC value of 3.1 μ g/ml when tested against *Candida albicans* Ca-15-3. Other compounds isolated from the same source are:



Compound	Isomer	Formula
265563	E	C ₂₅ H ₂₆ O ₅
265564	Z	C ₂₅ H ₂₆ O ₅

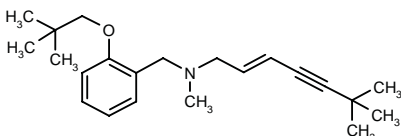
SOURCE – Shionogi.

REFERENCES

1. Jogakinai, T. et al. (Shionogi & Co. Ltd.) *Novel benzoxacyclotridecine cpds. and medical compsns. containing them*. JP 98101666.

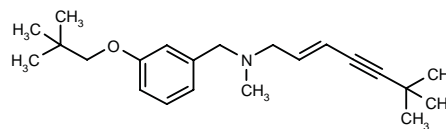
265248

N-[6,6-Dimethylhept-2(*E*)-en-4-ynyl]-*N*-[2-(2,2-dimethyl-propoxy)benzyl]-*N*-methylamine



C22 H33 N O; Mol wt: 327.5087

ACTION – Antifungal agent, an analog of terbinafine with MIC values of 50 μ g/ml when tested *in vitro* against *Trichophyton mentagrophytes* IFO7552 and *Trichophyton rubrum* IFO5808. Another related compound is:



265961: C22 H33 N O

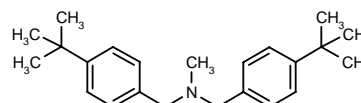
SOURCE – Pola Chemical.

REFERENCES

1. Ito, T. et al. (Pola Chemical Industries Inc.) *Antifungal agents*. JP 98139739.

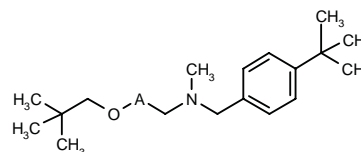
265249

N,N-Bis(4-*tert*-butylbenzyl)-*N*-methylamine



C23 H33 N; Mol wt: 323.5207

ACTION – Antifungal agent with MIC values of 12.5, 6.25, 6.25, 6.25 and 100 μ g/ml when tested *in vitro* against *Trichophyton mentagrophytes* IFO5811, *Trichophyton rubrum* IFO5808, *Trichophyton violaceum* TIMM1264, *Microsporum gypseum* IFO8231 and *Microsporum canis* TIMM0760. Other exemplified compounds are:



Compound	A	Formula
265890	1,3-Ph	C ₂₄ H ₃₅ NO
265891	1,2-Ph	C ₂₄ H ₃₅ NO

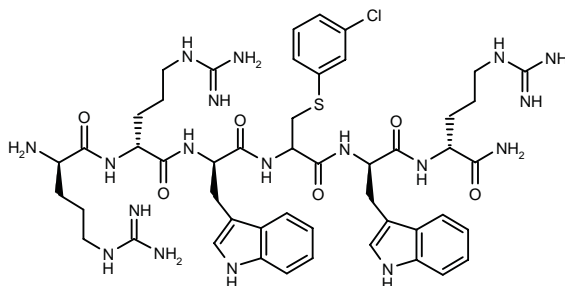
SOURCE – Pola Chemical.

REFERENCES

1. Kawatsu, Y. et al. (Pola Chemical Industries Inc.) *Antifungal agents*. JP 98139740.

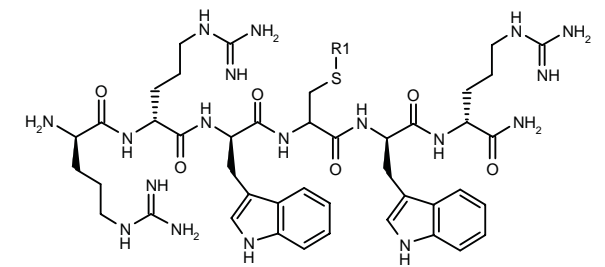
265281

D-Arginyl-D-arginyl-D-tryptophyl-DL-[*S*-(3-chlorophenyl)]-cysteinyl-D-tryptophyl-D-argininamide



C49 H67 Cl N18 O6 S; Mol wt: 1071.7070

ACTION – Antifungal agent with potent *in vitro* activity against *Candida albicans* ATCC 90028, giving an MIC value of 3.13 µg/ml compared to MIC values of 6.25, > 100 and 0.2 µg/ml for miconazole, fluconazole and amphotericin B, respectively. LD₅₀ = 500 mg/kg p.o. or more in mice. Other related peptides include the following:



Compound	R1	Isomer	Formula
265957	4-Br-Ph	DL	C ₄₉ H ₆₇ BrN ₁₈ O ₆ S
265958	4-Cl-PhCH ₂	DL	C ₅₀ H ₆₉ ClN ₁₈ O ₆ S
265959	4-Cl-PhCH ₂	D	C ₅₀ H ₆₉ ClN ₁₈ O ₆ S
265960	4-Cl-PhCH ₂	L	C ₅₀ H ₆₉ ClN ₁₈ O ₆ S

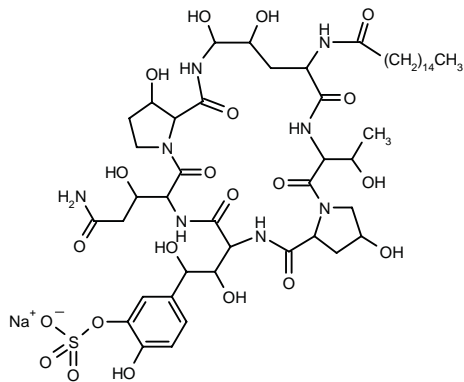
SOURCE – Morinaga Milk.

REFERENCES

1. Shimamura, S. et al. (Morinaga Milk Industry Co., Ltd.) *Peptide derivs. and antifungal agents*. JP 98114798.

265529

20-(2-Carbamoyl-1-hydroxyethyl)-23-[1,2-dihydroxy-2-(4-hydroxy-3-sulfooxyphenyl)ethyl]-9-(hexadecanamido)-2,11,12,15-tetrahydroxy-6-(1-hydroxyethyl)perhydrodipyrrolo[2,1-c:2',1'-]-1,4,7,10,13,16-hexaazacyclohene-icosine-5,8,14,19,22,25-hexaone



C50 H79 N8 Na O21 S; Mol wt: 1183.2650

ACTION – Antifungal agent, an inhibitor of β-1,3-glucan synthase isolated from a culture of *Coleophoma* sp. F-11899 (FERM BP-2635), with MEC (minimum effective concentration) values of 0.04 and 0.08 µg/ml, respectively, against *Candida albicans* FP633 and *Aspergillus fumigatus* FP1305. Also reported to be useful for the treatment of *Pneumocystis carinii* infections.

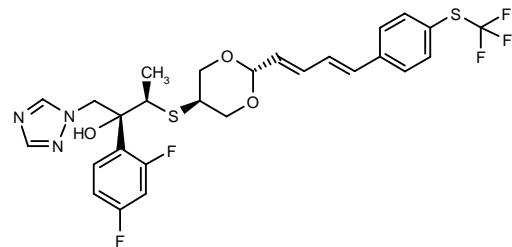
SOURCE – Fujisawa.

REFERENCES

1. Kanasaki, R. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Cyclic hexapeptides having antibiotic activity*. WO 9822498.

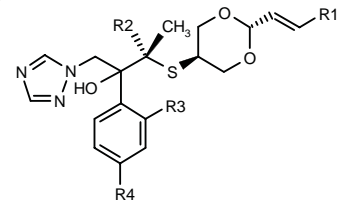
265912

trans-2-(*R*)-(2,4-Difluorophenyl)-1-(1,2,4-triazol-1-yl)-3(*R*)-[2-[4-[4-(trifluoromethylsulfanyl)phenyl]-1(*E*),3(*E*)-butadienyl]-1,3-dioxan-5-ylsulfanyl]-2-butanol

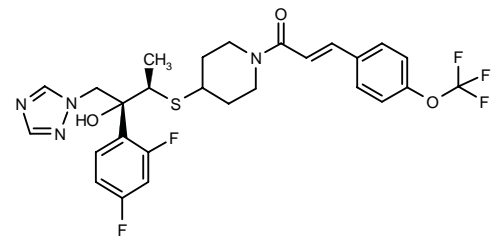


C27 H26 F5 N3 O3 S2; Mol wt: 599.6424

ACTION – Orally active azole antifungal agent, as demonstrated in a murine model of systemic candidosis by a 100% survival rate at day 21 postinfection in animals given a dose of 20 mg/kg p.o. compared to a survival rate of 60% for fluconazole at the same dose. Other compounds from this series of triazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
266661	4-CF ₃ -Ph	Me	H	CF ₃	C ₂₇ H ₂₇ F ₆ N ₃ O ₃ S
266662	(<i>E</i>)-4-(CF ₃ SO)-Ph-CH=CH	H	F	F	C ₂₇ H ₂₆ F ₅ N ₃ O ₄ S ₂
266663	(<i>E,E</i>)-4-CF ₃ -Ph-CH=CHCH=CH	H	F	F	C ₂₉ H ₂₈ F ₅ N ₃ O ₃ S



266660: C27 H27 F5 N4 O3 S

SOURCE – Sankyo.

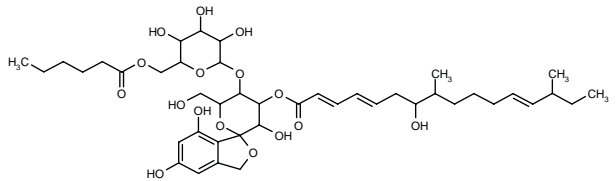
REFERENCES

1. Oida, S. et al. (Sankyo Co., Ltd.) *Medicines containing triazole derivs.* JP 98158167.

F-10748D1

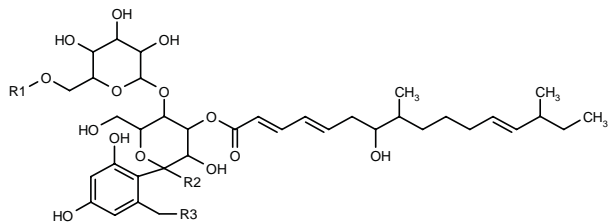
265276

7-Hydroxy-8,14-dimethylhexadeca-2,4,12-trienoic acid 5-(6-*O*-hexanoylaldohexopyranosyloxy)-3,5,7-trihydroxy-6-(hydroxymethyl)spiro[isobenzofuran-1(3*H*),2-tetrahydropyran]-4-yl ester



C43 H64 O16; Mol wt: 836.9626

ACTION – Antifungal agent isolated from *Lophodermium* sp. SANK 18496 (FERM BP-5620), active *in vitro* against yeasts such as *Candida albicans* ATCC 90028 (MIC = 0.5 µg/ml) and *Candida parapsilosis* ATCC 90018 (MIC = 0.5 µg/ml). Compound was found to inhibit 1,3-β-glucan synthase from *Aspergillus fumigatus* (IC₅₀ = 0.2 µg/ml). Other compounds isolated from this source are:



Compound	R1	R2	R3	Formula
F-10748C1 [265947]	COBu	-O-		C ₄₂ H ₆₂ O ₁₆
F-10748C2 [265948]	COBu	H	OH	C ₄₂ H ₆₄ O ₁₆
F-10748B1 [265949]	COPr	-O-		C ₄₁ H ₆₀ O ₁₆
F-10748B2 [265950]	COPr	H	OH	C ₄₁ H ₆₂ O ₁₆
F-10748D2 [265951]	COC5H11	H	OH	C ₄₃ H ₆₆ O ₁₆
F-10748A1 [265952]	H	-O-		C ₃₇ H ₅₄ O ₁₅
F-10748A2 [265953]	H	H	OH	C ₃₇ H ₅₆ O ₁₅

SOURCE – Sankyo.

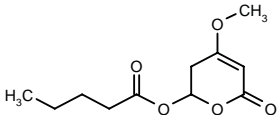
REFERENCES

1. Miyakoshi, S. et al. (Sankyo Co., Ltd.) *Novel antifungal cpds.* JP 98114786.

TKR-2648

265488

Pentanoic acid 4-methoxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl ester



C11 H16 O5; Mol wt: 228.2424

ACTION – Antifungal and antimetastatic agent isolated from *Penicillium* sp. TKR2648 (FERM BP-6093) with antifungal and antiproliferative activity. Compound exhibited MIC values of 100, 50, 3.13 and 6.25 µg/ml when tested against *Candida albicans* TIMM0136,

Candida kefir TIMM0301, *Cryptococcus neoformans* TIMM0354 and *Aspergillus fumigatus* TIMM1766. Antimetastatic activity was demonstrated in mice inoculated with EL4 lymphoma (liver) and B16 melanoma (lung) cells. No toxicity was observed following administration of 50 mg/kg i.p. to mice.

SOURCE – Takara Shuzo.

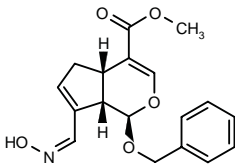
REFERENCES

1. Takesako, K. et al. (Takara Shuzo Co., Ltd.) *Antibiotic TKR2648 and process for producing the same.* WO 9821196.

ANTIVIRAL DRUGS

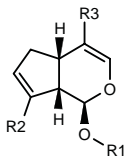
264887

(1*R*,4*aS*,7*aS*)-1-Benzyloxy-7-(hydroxyiminomethyl)-1,4*a*,5,7*a*-tetrahydrocyclopenta[*c*]pyran-4-carboxylic acid methyl ester



C18 H19 N O5; Mol wt: 329.3501

ACTION – Agent for the treatment of hepatitis B virus (HBV) infection, giving an ED₅₀ value of 15 µM when assessed *in vitro* for inhibition of HBV replication in 2.2.15 cells (ED₅₀ ddC = 15 µM). Compound showed low cytotoxic potential in uninfected cells (IC₅₀ = 130 µM; IC₅₀ ddC > 30 µM). Within this series of genipin derivatives, the following are also included:



Compound	R1	R2	R3	Formula
265772	Me	CH=NOH	4-MeO-Ph-CH2OCH2	C ₁₉ H ₂₃ NO ₅
265773	4-Pyr-CO	4-Pyr-COOCH2	CO2Me	C ₂₃ H ₂₀ N ₂ O ₇
265774	CH2Ph	CHO	CO2Me	C ₁₈ H ₁₈ O ₅

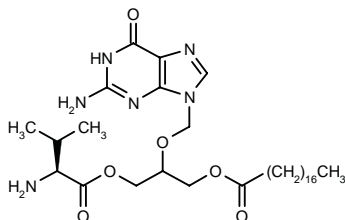
SOURCE – Choongwae.

REFERENCES

1. Moon, S.H. et al. (Choongwae Pharma Corp.) *Novel genipin deriv. having anti hepatitis B virus activity.* WO 9817663.

265497

9-[2-(Octadecanoyloxy)-1-(L-valyloxymethyl)ethoxymethyl]guanine



C32 H56 N6 O6; Mol wt: 620.8304

ACTION – Antiviral nucleoside, a prodrug of ganciclovir with improved oral bioavailability (47.8% vs. 10.6% for ganciclovir in rats). A representative compound from a series of mixed ester prodrugs of antiviral nucleosides.

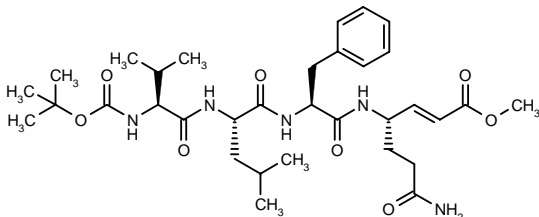
SOURCE – Medivir.

REFERENCES

1. Zhou, X.-X. and Johansson, N.-G. (Medivir AB) *Nucleosides*. WO 9821223.

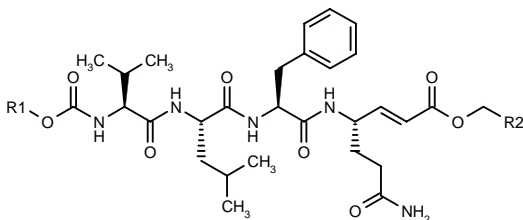
266052

4(S)-(tert-Butoxycarbonyl-L-valyl-L-leucyl-L-phenylalanyl-amino)-6-carbamoyl-2(E)-hexenoic acid methyl ester



C33 H51 N5 O8; Mol wt: 645.7929

ACTION – Antiviral agent, an inhibitor of human rhinovirus 3C protease ($IC_{50} = 0.25 \pm 0.02 \mu M$ against recombinant HRV-14 enzyme) proven effective in inhibiting virus replication ($IC_{50} = 0.74 \mu g/ml$ in the plaque reduction assay in HRV-14-infected HeLa cells), with little cytotoxicity in uninfected cells. Other peptidyl Michael acceptors with similar pharmacological profiles are:



Compound	R1	R2	Formula
266053	t-Bu	Me	C ₃₄ H ₅₃ N ₅ O ₈
266054	CH ₂ Ph	H	C ₃₆ H ₄₉ N ₅ O ₈

SOURCE – Lilly.

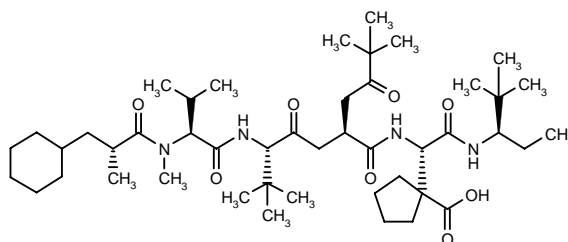
REFERENCES

1. Kong, J. et al. *Synthesis and evaluation of peptidyl Michael acceptors that inactivate human rhinovirus 3C protease and inhibit virus replication*. J Med Chem 1998, 41(14): 2579.

BILD-1633-SE*

247640

1-[1(S)-[5(S)-[N-[3-Cyclohexyl-2(R)-methylpropionyl]-N-methyl-L-valylamino]-6,6-dimethyl-4-oxo-2(R)-(pivaloyl-methyl)heptanamido]-1-[N-[1(R)-ethyl-2,2-dimethyl-propyl]carbamoyl]methyl]cyclopentane-1-carboxylic acid



C46 H80 N4 O8; Mol wt: 817.1580

ACTION – Antiviral agent, a peptidomimetic inhibitor of herpes simplex virus (HSV) ribonucleotide reductase proven to be more potent than aciclovir *in vitro* against wild-type and aciclovir-resistant HSV mutants ($EC_{50} = 0.14-0.45 \mu M$ vs. $2.7-60.2 \mu M$ for aciclovir). *In vivo*, topical treatment with BILD-1633-SE (5%) significantly reduced cutaneous lesions in athymic nude mice infected with the aciclovir-resistant isolates HSV type 1 (HSV-1) *d/sptk* and PAA'5; combination therapy with topical BILD-1633-SE (5%) and aciclovir in the drinking water (5 mg/ml) was more effective than either agent alone in both infection models.

SOURCE – Boehringer Ingelheim.

REFERENCES

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*Identified compound **247640** Drug Data Report 1997, 019(05): 0443.

PALIVIZUMAB

218833

Immunoglobulin G₁ (human-mouse monoclonal MEDI-493 γ 1-chain anti-respiratory syncytial virus protein F), disulfide with human-mouse monoclonal MEDI-493 κ -chain, dimer

MEDI-493

ACTION – Humanized monoclonal antibody to the F protein of respiratory syncytial virus (RSV) with broad neutralizing activity against RSV A and B subtypes *in vitro*; it produced a 99% reduction in lung RSV titers in cotton rats at a dose of 2.5-5 mg/kg.

INDICATION – Prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk.

PRESENTATION – Single-use vials containing sterile, lyophilized powder for reconstitution with sterile water for injection, 100 mg.

PROPRIETARY NAME – Synagis (US).

SOURCES – Abbott; MedImmune.

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21. *MedImmune completes patient enrollment in phase 3 trial of monoclonal antibody for respiratory syncytial virus*. MedImmune, Inc. Press Release 1996, Dec 16.

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25. *MedImmune reports third set of clinical results evaluating MEDI-493*. MedImmune, Inc. Press Release 1997, April 8.

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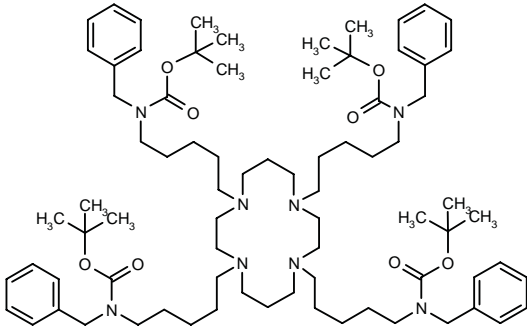
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MONOGRAPH – Sorbera, L.A. et al. *Palivizumab*. Drugs Fut 1998, 023(09): 0970.

AIDS MEDICINES

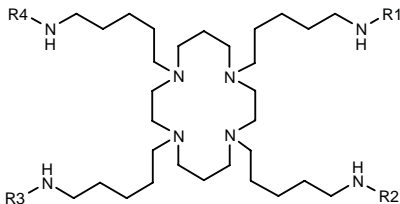
252673^{1,2}

N,N',N'',N'''-(1,4,8,11-Tetraazacyclotetradecan-1,4,8,11-tetrayl)tetrakis(pentane-1,5-diyl)tetrakis(N-benzylcarbamic acid *tert*-butyl ester)



C78 H124 N8 O8 ; Mol wt: 1301.8860

ACTION – Potent anti-HIV agent proven to inhibit syncytium formation in HIV-1-infected MT-4 cells with an EC₅₀ of 1 ± 0.5 µM, while having low cytotoxicity in mock-infected cells (CC₅₀ > 10 µM); it was inactive against duck hepatitis B virus (DHBV) and was cytotoxic to duck hepatocytes (CC₅₀ = 5 µM). Time course studies indicated that the compound interferes with a replicative process following virus adsorption but preceding reverse transcription. Other compounds from this series of N,N',N'',N'''-tetrakis(ω-aminoalkyl)tetraazamacrocycles with significant activity against HIV-1 and/or DHBV are:



Compound	R1=R2=R3=R4	Formula
260816 ¹	CH2Ph	C ₅₈ H ₈₂ N ₈
260818 ¹	H	C ₃₀ H ₆₈ N ₈

SOURCE – INSERM, Marseille (FR).

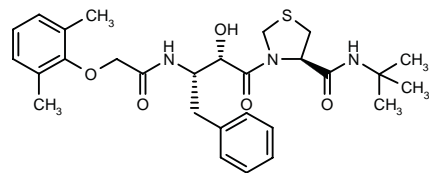
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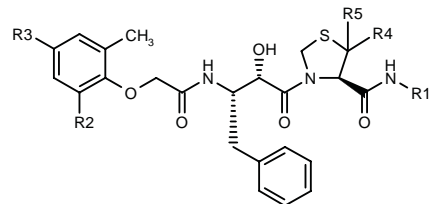
264352

N-*tert*-Butyl-3-[3(*S*)-[2-(2,6-dimethylphenoxy)acetamido]-2(*S*)-hydroxy-4-phenylbutyryl]thiazolidine-4(*R*)-carboxamide



C28 H37 N3 O5 S; Mol wt: 527.6823

ACTION – Orally bioavailable antiviral agent for AIDS, an inhibitor of HIV protease (56.4% inhibition at 50 nM; 95.2% inhibition at 5 μM) with potent activity against HIV in MT-4 cells (EC₅₀ = 1.40 μg/ml) and low cytotoxicity in uninfected cells (CC₅₀ = 320 μg/ml). Other compounds from this series of dipeptide derivatives include the following:



Compound	R1	R2	R3	R4=R5	Formula
267055	t-Bu	Me	Me	H	C ₂₉ H ₃₉ N ₃ O ₅ S
267056	2-Me-PhCH2	Me	H	H	C ₃₂ H ₃₇ N ₃ O ₅ S
267057	2-Me-PhCH2	Me	NH2	H	C ₃₂ H ₃₈ N ₄ O ₅ S
267058	t-Bu	Me	NH2	Me	C ₃₀ H ₄₂ N ₄ O ₅ S
267059	t-Bu	Me	CHO	Me	C ₃₁ H ₄₁ N ₃ O ₆ S
267060	t-Bu	Me	CONH2	Me	C ₃₁ H ₄₂ N ₄ O ₆ S
267061	t-Bu	NH2	Me	Me	C ₃₀ H ₄₂ N ₄ O ₅ S

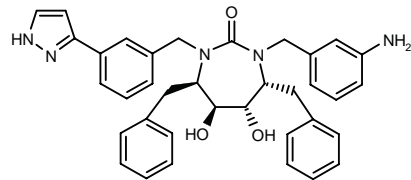
SOURCE – Japan Energy.

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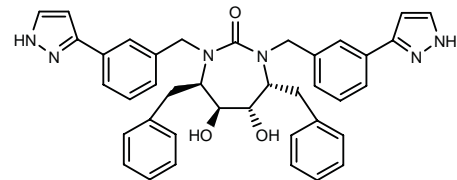
265340

[4*R*-(4α,5α,6β,7β)]-1-(3-Aminobenzyl)-4,7-dibenzyl-5,6-dihydroxy-3-[3-(3(5)-pyrazolyl)benzyl]perhydro-1,3-diazepin-2-one



C36 H37 N5 O3; Mol wt: 587.7203

ACTION – Highly potent, orally bioavailable cyclic HIV protease inhibitor with a K_i value of 0.035 nM, potent antiviral activity in HIV-1-infected MT-2 cells (IC₉₀ = 27 nM in an RNA assay) and low cytotoxicity (TC₅₀ = 6.8 μM). It shows good metabolic stability and good oral bioavailability in dogs, giving a peak plasma concentration of 0.85 μM at a dose of 2.5 mg/kg p.o. Another related compound is:



265339: C39 H38 N6 O3

SOURCE – DuPont Pharm.

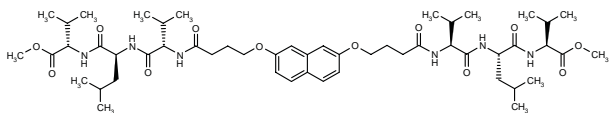
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265412

N,N'-(Naphthalene-2,7-diylloxy)bis(1-oxobutane-4,1-diyl)bis(valyl-leucyl-valine methyl ester)



C52 H82 N6 O12; Mol wt: 983.2498

ACTION – Structurally simple HIV-1 protease dimerization inhibitor designed to interact with the C-terminal end of each HIV-1 protease monomer to prevent the formation of the active dimer.

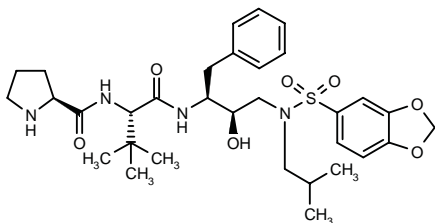
SOURCES – CNRS, Chatenay-Malabry (FR); Univ. Paris VI & VII Paris (FR).

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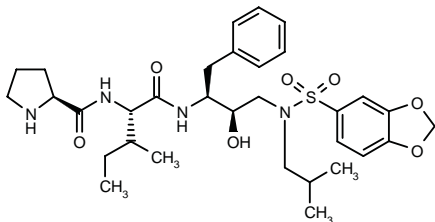
265873

N-[3-[*N*-(1,3-Benzodioxol-5-ylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]-3,3-dimethyl-2(*S*)-[pyrrolidin-2(*S*)-ylcarboxamido]butyramide



C32 H46 N4 O7 S; Mol wt: 630.8024

ACTION – Antiviral agent for AIDS, an inhibitor of retroviral proteases, particularly HIV protease (IC_{50} = 2 nM), with potent anti-HIV-1 activity in infected CEM cells (EC_{50} = 12 nM). Another compound from this series of hydroxyethylamino sulfonamide derivatives is:



266132: C32 H46 N4 O7 S

SOURCE – Searle.

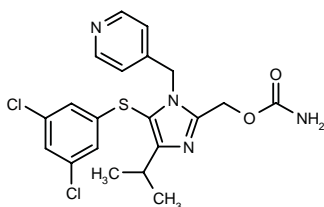
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S-1153***256200**

Carbamic acid 5-(3,5-dichlorophenylsulfonyl)-4-isopropyl-1-(4-pyridylmethyl)imidazol-2-ylmethyl ester

AG-1549



C20 H20 Cl2 N4 O2 S; Mol wt: 451.3760

ACTION – Orally active imidazole compound that inhibits HIV-1 reverse transcriptase, with potent activity against both wild-type enzyme and mutants with single amino acid substitutions responsible for resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs; EC_{50} = 0.3-7 ng/ml). It showed potent activity against different laboratory strains of HIV-1 in several cell lines (EC_{50} = 0.51-2.1 ng/ml), as well as against zidovudine-sensitive and -resistant clinical isolates (EC_{90} = 6.6-10 ng/ml). The emergence of resistance to S-1153 was slower than for nevirapine, at least two mutations were required for

resistance, and S-1153-resistant variants remained sensitive to zidovudine and lamivudine. In a mouse-MT-4 cell HIV replication model, combination of S-1153 and zidovudine administered orally demonstrated marked synergy. The compound was also shown to significantly accumulate in lymph nodes. It appears to be a suitable candidate for two- or three-drug combination therapy of HIV infection, and clinical trials are in progress.

SOURCES – Agouron; Shionogi.

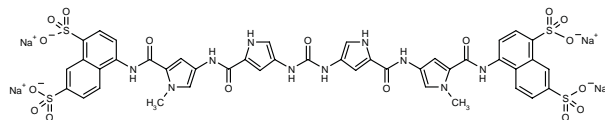
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8. Agouron Pharmaceuticals, Inc. Product Pipeline 1998, June 30.

*Identified compound **256200** Drug Data Report 1998, 020(03): 0248.

NSC-651016**236868**

4,4'-[Carbonylbis[imino(1*H*-pyrrole-4,2-diyl)carbonyl-imino(1-methyl-1*H*-pyrrole-4,2-diyl)carbonylimino]]bis(1,7-naphthalenedisulfonic acid) tetrasodium salt



C43 H32 N10 Na4 O17 S4; Mol wt: 1181.0030

ACTION – Anti-HIV agent, a chemokine receptor antagonist that selectively inhibits chemokine binding to CCR1, CCR3, CCR5 and CXCR4, but not to CXCR2 or CCR2b receptors, and blocks chemokine-induced intracellular calcium flux. Title compound inhibited the replication of a range of laboratory strains and clinical isolates of HIV-1 including drug-resistant isolates (EC_{50} = 1.2-7.2 μ M), as well as HIV-2 (EC_{50} = 13.9 μ M) and SIV (EC_{50} = 26.0 μ M); it exhibited *in vivo* activity in an SCID mouse hollow fiber model, inhibiting the acute replication of HIV-1 in CEM-SS cells, showing a synergistic interaction with zidovudine in this model and no significant toxicity at effective antiviral doses. NSC-651016 is under evaluation as a potential salvage therapy in patients who do not tolerate or who have developed resistance to available anti-HIV therapies, as well as for use as an intravaginal microbicide to block the sexual transmission of HIV.

SOURCES – NCI, Bethesda, MD (US); University of Vermont, Burlington, VT (US).

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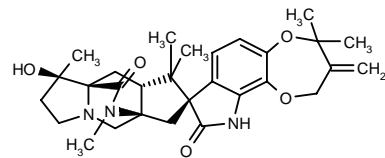
3. Howard, O.M.Z. et al. *Inhibition of in vitro and in vivo HIV replication by a distamycin analogue that interferes with chemokine receptor function: A candidate for chemotherapeutic and microbicidal application.* J Med Chem 1998, 41(13): 2184.

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TREATMENT OF HELMINTHIC DISEASES

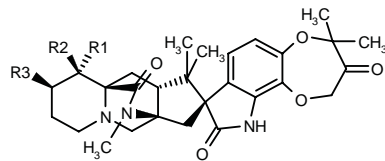
263809

(1'*R*,5'*aR*,7'*R*,8'*aR*,9'*aS*)-1'-Hydroxy-1',4,4,8',11'-hexamethyl-3-methylenespiro[3,4,9,10-tetrahydro-2*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7'-perhydro-5'*a*,9'*a*-(iminomethano)cyclopent[*f*]indolizine]-9,10'-dione



C29 H37 N3 O5; Mol wt: 507.6273

ACTION – Antiparasitic agent active against endo- and ectoparasites, particularly helminths and arthropods. Other specifically claimed compounds from this series of marcfortine and paraherquamide derivatives include the following:



Compound	R1	R2	R3	Formula
266835	H	H	H	C ₂₈ H ₃₅ N ₃ O ₅
266836	Me	OH	H	C ₂₉ H ₃₇ N ₃ O ₆
266837	H	OH	Me	C ₂₉ H ₃₇ N ₃ O ₆

SOURCE – Pharmacia & Upjohn.

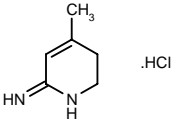
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TREATMENT OF SEPTIC SHOCK

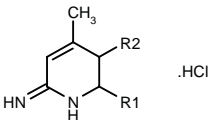
265262

4-Methyl-1,2,5,6-tetrahydropyridin-2-imine hydrochloride

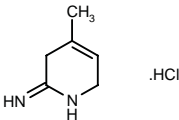


C6 H10 N2 . HCl; Mol wt: 146.6199

ACTION – Agent for the treatment or prevention of shock, rheumatoid arthritis, hypotension, ulcerative colitis, cerebral ischemia, insulin-dependent diabetes and cancer, an inhibitor of inducible nitric oxide synthase (iNOS; IC₅₀ = 0.02 μM in murine macrophage homogenates). Other compounds from this series of imine derivatives include the following:



Compound	R1	R2	Formula
265977	allyl	H	C ₉ H ₁₄ N ₂ .HCl
265978	cis-(CH ₂) ₃ -		C ₉ H ₁₄ N ₂ .HCl



265979: C6 H10 N2.HCl

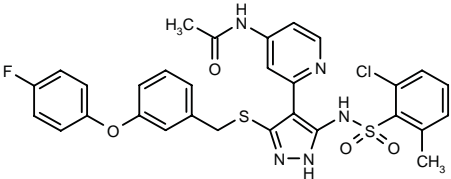
SOURCE – Ono.

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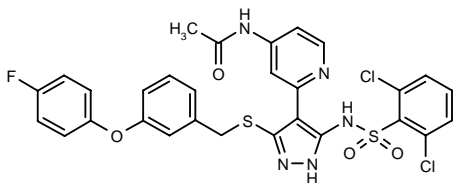
265429

N-[2-[5-(2-Chloro-6-methylphenylsulfonamido)-3-[3-(4-fluorophenoxy)benzylsulfanyl]-1*H*-pyrazol-4-yl]pyridin-4-yl]acetamide



C30 H25 Cl F N5 O4 S2; Mol wt: 638.1415

ACTION – Agent for the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis, an inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂). A representative compound from a series of specifically claimed pyrazoles, wherein the following are also included:



266253: C29 H22 Cl2 F N5 O4 S2

SOURCE – Lilly.

REFERENCES

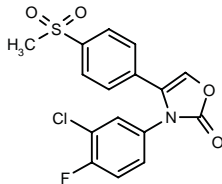
1. Doman, P.J. et al. (Eli Lilly and Company) *Pyrazoles as human non-pancreatic secretory phospholipase A₂ inhibitors*. EP 846687, WO 9824437.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

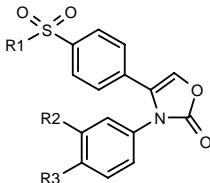
263843

3-(3-Chloro-4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-oxazol-2(3*H*)-one



C16 H11 Cl F N O4 S; Mol wt: 367.7829

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.366 μM vs. IC₅₀ > 300 μM for COX-1; COX-1/COX-2 > 819). *In vivo* antiinflammatory activity was demonstrated in rats in the carrageenan-induced paw edema test (ID₅₀ = 2.5 mg/kg p.o.) and analgesic activity in the kaolin-induced arthritis test (ED₅₀ = 4.1 mg/kg p.o.). Compound was shown to possess very low ulcerogenic potential in rats (UD₅₀ > 1000 mg/kg p.o.; UD₅₀ indomethacin = 8.3 mg/kg p.o.). Other specifically claimed compounds from this series of 3,4-diaryloxazolone derivatives include the following:



Compound	R1	R2	R3	Formula
266819	Me	Cl	Cl	C ₁₆ H ₁₁ Cl ₂ NO ₄ S
266820	Me	Cl	Me	C ₁₇ H ₁₄ ClNO ₄ S
266822	NH2	Cl	H	C ₁₅ H ₁₁ ClN ₂ O ₄ S
266823	NH2	H	Cl	C ₁₅ H ₁₁ ClN ₂ O ₄ S
266824	NH2	F	H	C ₁₆ H ₁₁ FN ₂ O ₄ S

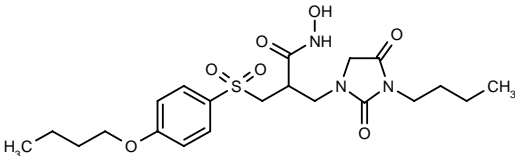
SOURCE – UPSA.

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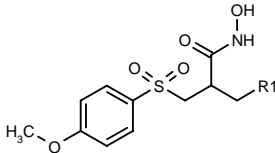
264382

2-(4-Butoxyphenylsulfonylmethyl)-3-(3-butyl-2,4-dioximidazolidin-1-yl)propionohydroxamic acid



C21 H31 N3 O7 S; Mol wt: 469.5559

ACTION – A potent inhibitor of matrix metalloproteinases such as gelatinase (K_i = 0.092 nM) and stromelysin (K_i = 1.8 nM) with potential in the treatment of disorders related to connective tissue degradation such as rheumatoid arthritis, osteoporosis, tumor metastasis, periodontitis, gingivitis and corneal, epidermal or gastric ulceration. Within this series of β-sulfonyl hydroxamic acids, the following are also included:



Compound	R1	Formula
266954	4-MeO-PhSO2	C ₁₈ H ₂₁ NO ₈ S ₂
266955	4-MeO-PhSO2CH2CH2	C ₂₀ H ₂₅ NO ₈ S ₂
266956	SO2C8H17	C ₁₉ H ₃₁ NO ₇ S ₂
266957	3-Bu-2,4-dioxo-1-imidazolidinyl	C ₁₈ H ₂₅ N ₃ O ₇ S

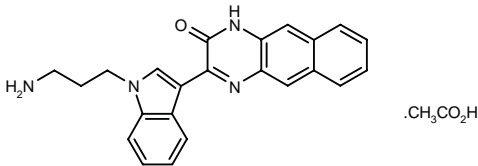
SOURCE – Pharmacia & Upjohn.

REFERENCES

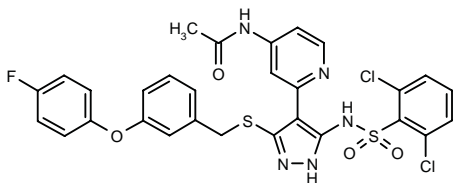
1. Warpehoski, M.A. and Harper, D.E. (Pharmacia AB) *β-Sulfonyl hydroxamic acids as matrix metalloproteinases inhibitors*. WO 9813340.

264390

3-[1-(3-Aminopropyl)indol-3-yl]benzo[*g*]quinoxalin-2(1*H*)-one acetate



C23 H20 N4 O . C2 H4 O2; Mol wt: 428.4896



266253: C29 H22 Cl2 F N5 O4 S2

SOURCE – Lilly.

REFERENCES

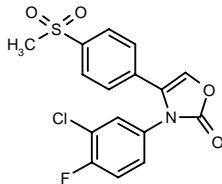
1. Doman, P.J. et al. (Eli Lilly and Company) *Pyrazoles as human non-pancreatic secretory phospholipase A₂ inhibitors*. EP 846687, WO 9824437.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

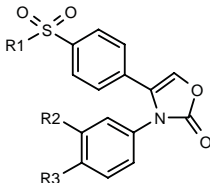
263843

3-(3-Chloro-4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-oxazol-2(3*H*)-one



C16 H11 Cl F N O4 S; Mol wt: 367.7829

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.366 μM vs. IC₅₀ > 300 μM for COX-1; COX-1/COX-2 > 819). *In vivo* antiinflammatory activity was demonstrated in rats in the carrageenan-induced paw edema test (ID₅₀ = 2.5 mg/kg p.o.) and analgesic activity in the kaolin-induced arthritis test (ED₅₀ = 4.1 mg/kg p.o.). Compound was shown to possess very low ulcerogenic potential in rats (UD₅₀ > 1000 mg/kg p.o.; UD₅₀ indomethacin = 8.3 mg/kg p.o.). Other specifically claimed compounds from this series of 3,4-diaryloxazolone derivatives include the following:



Compound	R1	R2	R3	Formula
266819	Me	Cl	Cl	C ₁₆ H ₁₁ Cl ₂ NO ₄ S
266820	Me	Cl	Me	C ₁₇ H ₁₄ ClNO ₄ S
266822	NH2	Cl	H	C ₁₅ H ₁₁ ClN ₂ O ₄ S
266823	NH2	H	Cl	C ₁₅ H ₁₁ ClN ₂ O ₄ S
266824	NH2	F	H	C ₁₆ H ₁₁ FN ₂ O ₄ S

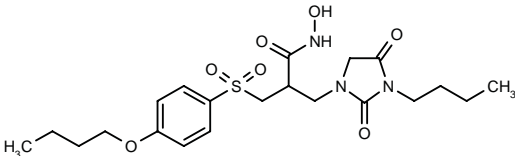
SOURCE – UPSA.

REFERENCES

1. Sartori, E. and Teulon, J.-M. (Laboratoires UPSA) *Novel 3,4-diaryloxazolone derivs., methods of preparation and therapeutic uses thereof*. WO 9811080.

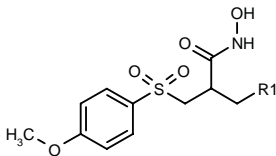
264382

2-(4-Butoxyphenylsulfonylmethyl)-3-(3-butyl-2,4-dioxoimidazolidin-1-yl)propionohydroxamic acid



C21 H31 N3 O7 S; Mol wt: 469.5559

ACTION – A potent inhibitor of matrix metalloproteinases such as gelatinase (K_i = 0.092 nM) and stromelysin (K_i = 1.8 nM) with potential in the treatment of disorders related to connective tissue degradation such as rheumatoid arthritis, osteoporosis, tumor metastasis, periodontitis, gingivitis and corneal, epidermal or gastric ulceration. Within this series of β-sulfonyl hydroxamic acids, the following are also included:



Compound	R1	Formula
266954	4-MeO-PhSO2	C ₁₈ H ₂₁ NO ₈ S ₂
266955	4-MeO-PhSO2CH2CH2	C ₂₀ H ₂₅ NO ₈ S ₂
266956	SO2C8H17	C ₁₉ H ₃₁ NO ₇ S ₂
266957	3-Bu-2,4-dioxo-1-imidazolidinyl	C ₁₈ H ₂₅ N ₃ O ₇ S

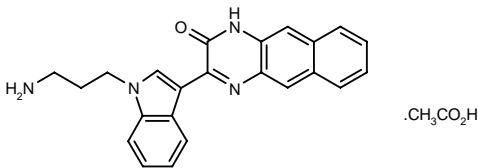
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Warpehoski, M.A. and Harper, D.E. (Pharmacia AB) *β-Sulfonyl hydroxamic acids as matrix metalloproteinases inhibitors*. WO 9813340.

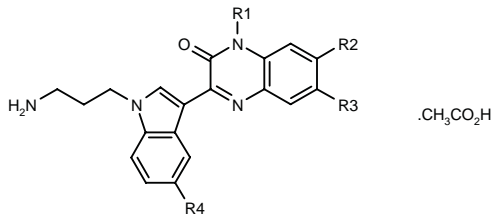
264390

3-[1-(3-Aminopropyl)indol-3-yl]benzo[*g*]quinoxalin-2(1*H*)-one acetate



C23 H20 N4 O . C2 H4 O2; Mol wt: 428.4896

ACTION – Agent for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular and neurodegenerative disorders and cancer that acts by inhibiting protein kinase C (PKC) and is also useful as an inhibitor of the production of cytokines such as IL-1 β , tumor necrosis factor (TNF- α), granulocyte–macrophage colony-stimulating factor (GM-CSF) or IL-8. A representative compound from a series of specifically claimed indole derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
267030	Me	H	H	H	C ₂₀ H ₂₀ N ₄ O.C ₂ H ₄ O ₂
267031	H	Cl	Cl	H	C ₁₉ H ₁₆ Cl ₂ N ₄ O.C ₂ H ₄ O ₂
267032	H	Cl	Cl	CO ₂ Me	C ₂₁ H ₁₈ Cl ₂ N ₄ O ₃ .C ₂ H ₄ O ₂
267033	Me	Cl	Cl	CO ₂ Me	C ₂₂ H ₂₀ Cl ₂ N ₄ O ₃ .C ₂ H ₄ O ₂
267034	H	H	OMe	CO ₂ Me	C ₂₂ H ₂₂ N ₄ O ₄ .C ₂ H ₄ O ₂
267035	t-BuOCOCH ₂	H	OMe	CO ₂ Me	C ₂₈ H ₃₂ N ₄ O ₆ .C ₂ H ₄ O ₂

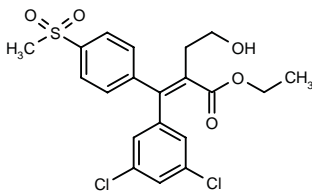
SOURCE – Astra.

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1. Bergstrand, H. et al. (Astra AB) *New pharmaceutically active cpds.* WO 9813368.

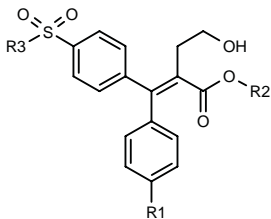
264427

2-[1-(3,5-Dichlorophenyl)-1-[4-(methylsulfonyl)phenyl]-methylene]-4-hydroxybutyric acid ethyl ester



C₂₀ H₂₀ Cl₂ O₅ S; Mol wt: 443.3450

ACTION – Antiinflammatory and analgesic agent, a selective inhibitor of cyclooxygenase type 2 (COX-2; 80 \pm 2% inhibition at 10 μ M vs. 0% inhibition of COX-1 at 10 μ M). *In vivo*, it was tested for antiinflammatory activity in rats in the carrageenan-induced paw edema model (28.9 \pm 4.5% inhibition at 30 mg/kg p.o.) and for analgesic activity in the kaolin-induced arthritis model (45.8 \pm 10.9% inhibition at 30 mg/kg p.o.). Other specifically claimed compounds from this series of diarylmethylene derivatives include the following:



Compound	R1	R2	R3	Formula
266964	F	Na	Me	C ₁₈ H ₁₆ FNaO ₅ S
266965	F	H	NH ₂	C ₁₇ H ₁₆ FNO ₅ S
266966	Cl	Na	Me	C ₁₈ H ₁₆ ClNaO ₅ S

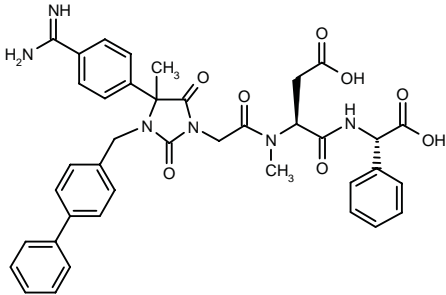
SOURCE – UPSA.

REFERENCES

1. Nicolai, E. and Teulon, J.-M. (Laboratoires UPSA) *Novel diarylmethylene derivs., method for preparing and therapeutic uses thereof.* WO 9815528.

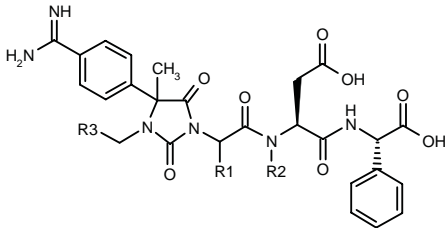
264671

N-[2-[4-(4-Amidinophenyl)-3-(4-biphenylmethyl)-4-methyl-2,5-dioximidazolidin-1-yl]acetyl]-*N*-methyl-L-aspartyl-L-phenylglycine



C₃₉ H₃₈ N₆ O₈; Mol wt: 718.7632

ACTION – Agent for the treatment or prevention of disorders involving leukocyte adhesion and migration and/or disorders involving adhesion processes mediated by the VLA-4 receptor such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the CNS, asthma, allergy, cardiovascular disorders, arteriosclerosis, restenosis, diabetes, transplant rejection, cancer and malaria. Compound was found to inhibit the adhesion of U937 cells to hVCAM-1(1-3)-Ig with an IC₅₀ value of 0.09 μ M. Other compounds from this series of 5-membered heterocycles include the following:



Compound	R1	R2	R3	Formula
266508	H	H	2-Naph	C ₃₆ H ₃₄ N ₆ O ₈
266509	H	H	4-Ph-Ph	C ₃₈ H ₃₆ N ₆ O ₈
266510	H	Me	Ph	C ₃₃ H ₃₄ N ₆ O ₈
266511	H	H	2-Naph	C ₃₆ H ₃₄ N ₆ O ₈
266512	Me	H	Ph	C ₃₃ H ₃₄ N ₆ O ₈
266513	H	H	Ph	C ₃₂ H ₃₂ N ₆ O ₈

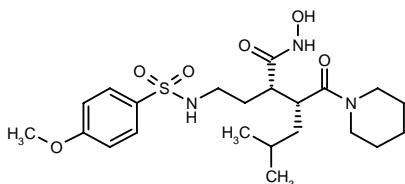
SOURCE – Hoechst Marion Roussel.

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1. Stilz, H.U. et al. (Hoechst AG) *5-Ring heterocycles as inhibitors of leukocyte adhesion and as VLA-4 antagonists*. EP 842943, JP 98147573.

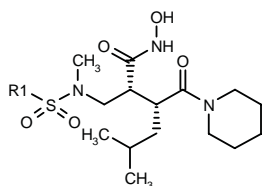
264882

2(S)-[2-(4-Methoxyphenylsulfonamido)ethyl]-5-methyl-3(R)-(piperidin-1-ylcarbonyl)hexanehydroxamic acid



C22 H35 N3 O6 S; Mol wt: 469.5995

ACTION – An inhibitor of matrix metalloproteinases with selectivity for collagenases such as human fibroblast collagenase (IC₅₀ = 50 nM) over gelatinases, stromelysins and matrilysin. Claimed for the treatment of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, cancer and neuroinflammatory disorders. Other compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	Formula
266063	4-MeO-Ph	C ₂₂ H ₃₅ N ₃ O ₆ S
266064	4-Me-Ph	C ₂₂ H ₃₅ N ₃ O ₆ S
266065	5-N(Me)2-1-Naph	C ₂₇ H ₄₀ N ₄ O ₆ S
266066	2-Naph	C ₂₆ H ₃₅ N ₃ O ₆ S
266067	CH2Ph	C ₂₂ H ₃₅ N ₃ O ₆ S
266068	4-BuO-Ph	C ₂₆ H ₄₁ N ₃ O ₆ S
266069	4-Ph-Ph	C ₂₇ H ₃₇ N ₃ O ₆ S

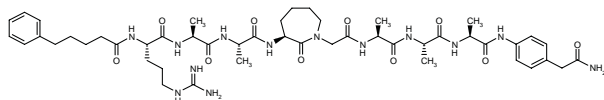
SOURCE – British Biotech.

REFERENCES

1. Beckett, R.P. et al. (British Biotech plc) *Metalloproteinase inhibitors*. WO 9817655.

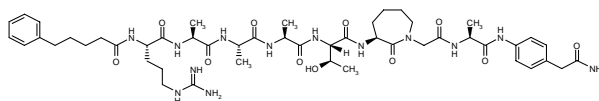
264893

2-[4-[N-[2-[2-Oxo-3(S)-(5-phenylpentanoyl-L-arginyl-L-alanyl-L-alanylamino)perhydroazepin-1-yl]acetyl]-L-alanyl-L-alanyl-L-alanylamino]phenyl]acetamide



C48 H71 N13 O10; Mol wt: 990.1699

ACTION – Agent for the treatment of autoimmune diseases and inflammatory disorders such as rheumatoid arthritis and multiple sclerosis, a peptide that binds to major histocompatibility complex (MHC) class II molecules and inhibits T-cell activation by selfantigens characteristic of autoimmune diseases. *In vitro*, compound was found to bind to purified HLA-DR peptides such as HLA-DR4Dw4, HL-DR1 and HLA-DR2, but not HLA-DR3. *In vivo*, it was active in a delayed-type hypersensitivity model in mice at a dose < 0.1 mg/kg/day when administered using osmotic minipumps. Compound is reported to possess good aqueous stability at pH 3 and 7.6. Another specifically claimed peptide is:



266039: C49 H73 N13 O11

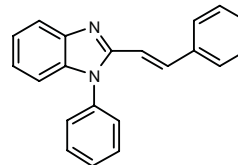
SOURCE – Zeneca.

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1. Luke, R.W.A. and Cotton, R. (Zeneca Ltd.) *Peptide analogues containing a 7-membered lactam ring*. WO 9817680.

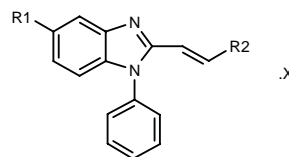
265431

1-Phenyl-2-[2(E)-phenylvinyl]benzimidazole



C21 H16 N2; Mol wt: 296.3714

ACTION – Antiinflammatory and analgesic agent, an inhibitor of cyclooxygenase (COX) with at least 10-fold selectivity for COX-2 relative to COX-1. Within this series of benzimidazole derivatives, the following are also specifically claimed:



Compound	R1	R2	X	Formula
266526	NO2	Ph		C ₂₁ H ₁₅ N ₃ O ₂
266527	CN	Ph		C ₂₂ H ₁₅ N ₃
266528	H	cyclopentyl	HCl	C ₂₀ H ₂₀ N ₂ ·HCl

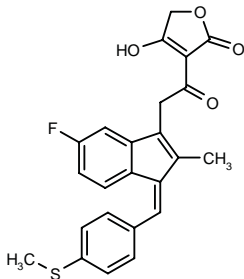
SOURCE – Pfizer.

REFERENCES

1. Mano, T. et al. (Pfizer Inc.) *Benzimidazole cpds*. EP 846689, JP 98168066.

265487

3-[2-[5-Fluoro-2-methyl-1-[4-(methylsulfanyl)benzyl-idene]inden-3-yl]acetyl]-4-hydroxyfuran-2(5*H*)-one



C24 H19 F O4 S; Mol wt: 422.4741

ACTION – Antiinflammatory agent, a potent inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.027 μM using recombinant human enzyme) with selectivity over COX-1 (100% inhibition at 10 μM using purified sheep enzyme). Also claimed for the treatment of colorectal cancer and Alzheimer's disease.

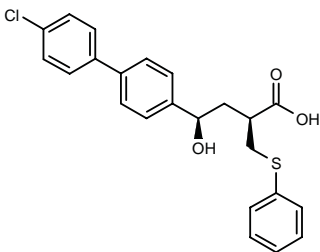
SOURCE – American Home Products.

REFERENCES

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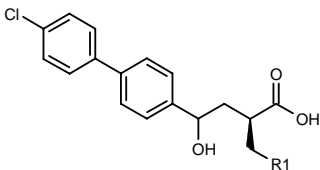
265513

(2*S*,4*R*)-4-(4'-Chlorobiphenyl-4-yl)-4-hydroxy-2-(phenyl-sulfanylmethyl)butyric acid



C23 H21 Cl O3 S; Mol wt: 412.9349

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as gelatinase A (MMP-2; IC₅₀ = 2.8 nM), gelatinase B (MMP-9; IC₅₀ = 58 nM) and stromelysin (MMP-3; IC₅₀ = 34 nM), claimed for the treatment of osteoarthritis, rheumatoid arthritis, periodontal disease, corneal ulceration, tumor metastasis and other MMP-mediated disorders. Within this series of 4-biphenyl-4-hydroxybutyric acid derivatives, the following are also included:



Compound	R1	Isomer	Formula
266463	SPh	S	C ₂₃ H ₂₁ ClO ₃ S
266464	CH ₂ CH ₂ Ph	R	C ₂₅ H ₂₅ ClO ₃
266465	CH ₂ CH ₂ Ph	S	C ₂₅ H ₂₅ ClO ₃

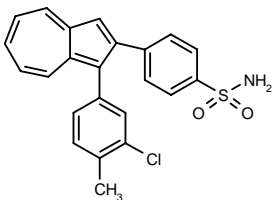
SOURCE – Bayer.

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1. Kluender, H.C.E. et al. (Bayer AG) *Substd. 4-biphenyl-4-hydroxybutyric acid derivs. as matrix metalloprotease inhibitors*. WO 9822436.

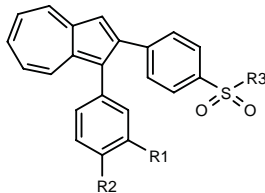
265915

4-[1-(3-Chloro-4-methylphenyl)azulen-2-yl]benzenesul-fonamide



C23 H18 Cl N O2 S; Mol wt: 407.9192

ACTION – Antiinflammatory and analgesic agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2; IC₅₀ = 0.0026 μM using purified enzyme from sheep placenta) as compared to COX-1 (IC₅₀ = 4.1 μM using purified enzyme from sheep seminal vesicles). Other compounds from this series of azulene derivatives include the following:



Compound	R1	R2	R3	Formula
266642	H	H	Me	C ₂₃ H ₁₈ O ₂ S
266643	Cl	H	Me	C ₂₃ H ₁₇ ClO ₂ S
266644	H	Cl	Me	C ₂₃ H ₁₇ ClO ₂ S
266645	Me	H	Me	C ₂₄ H ₂₀ O ₂ S
266646	Cl	F	Me	C ₂₃ H ₁₆ ClFO ₂ S
266647	Cl	Me	Me	C ₂₄ H ₁₉ ClO ₂ S
266648	Cl	OMe	Me	C ₂₄ H ₁₉ ClO ₃ S
266649	H	H	NH ₂	C ₂₂ H ₁₇ NO ₂ S
266650	Cl	F	NH ₂	C ₂₂ H ₁₅ ClFNO ₂ S
266651	Cl	OMe	NH ₂	C ₂₃ H ₁₈ ClNO ₃ S
266652	F	OMe	NH ₂	C ₂₃ H ₁₈ FNO ₃ S
266653	OMe	OMe	Me	C ₂₅ H ₂₂ O ₄ S

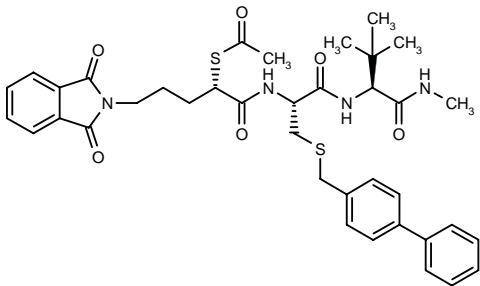
SOURCE – Kotobuki.

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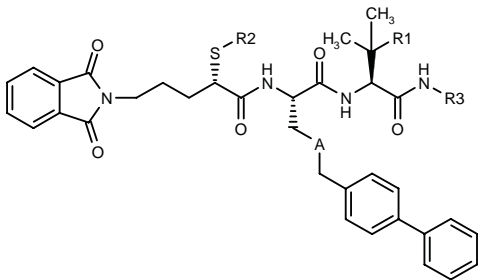
266175

N-[2(S)-(Acetylsulfanyl)-5-phthalimidopentanoyl]-L-(S-biphenyl-4-ylmethyl)cysteiny-L-(3-methyl)valine methylamide

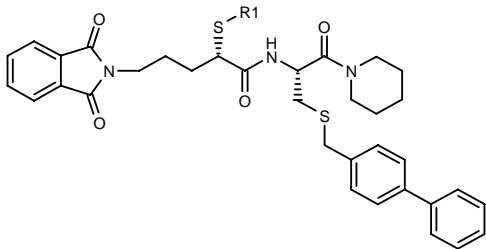


C38 H44 N4 O6 S2; Mol wt: 716.9196

ACTION – An inhibitor of matrix metalloproteinases (MMPs) with potential in the treatment of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration and cancer. Other compounds from this series of α -mercaptoamide derivatives include the following:



Compound	R1	R2	R3	A	Formula
266880	SCH2Ph	Ac	Me	-S-	C ₄₄ H ₄₈ N ₄ O ₆ S ₃
266881	Me	Ac	Me	-SO2-	C ₃₈ H ₄₄ N ₄ O ₆ S ₂
266882	Me	H	Me	-S-	C ₃₆ H ₄₂ N ₄ O ₅ S ₂
266883	SCH2Ph	H	Me	-S-	C ₄₂ H ₄₆ N ₄ O ₅ S ₃
266884	Me	H	Me	-SO2-	C ₃₆ H ₄₂ N ₄ O ₇ S ₂
266885	Me	Ac	4-Pyr	-S-	C ₄₂ H ₄₅ N ₅ O ₆ S ₂
266886	Me	H	4-Pyr	-S-	C ₄₀ H ₄₃ N ₅ O ₅ S ₂



Compound	R1	Formula
266887	Ac	C ₃₆ H ₃₉ N ₃ O ₅ S ₂
266888	H	C ₃₄ H ₃₇ N ₃ O ₄ S ₂

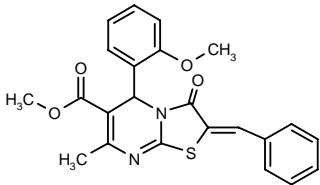
SOURCE – British Biotech.

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1. Floyd, C.D. (British Biotech plc) *Metalloproteinase inhibitors*. WO 9823588.

266261

5-(2-Methoxyphenyl)-7-methyl-3-oxo-2(Z)-benzylidene-5H-1,3-thiazolo[3,2-a]pyrimidine-6(3H)-carboxylic acid methyl ester



C23 H20 N2 O4 S; Mol wt: 420.4870

M.p. 193-4 °C.

ACTION – The most potent antiinflammatory agent from a series of 2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl esters, as demonstrated in the carrageenan-induced paw edema assay in mice (ED₅₀ = 10.37 mg/kg p.o.), being significantly more potent than aspirin (ED₅₀ = 79.39 mg/kg p.o.) and indomethacin (ED₅₀ = 25.99 mg/kg p.o.); the incidence of ulcers (5/8 animals at 100 mg/kg p.o.) was similar to with aspirin (4/8 animals at this dose), but less than with indomethacin (8/8 animals at this dose).

SOURCES – Hacettepe University, Ankara (TR); Westfälische Wilhelms-Universität, Münster (DE).

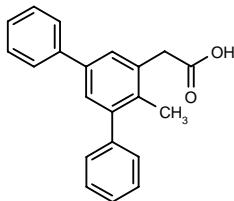
REFERENCES

1. Tozkoparan, B. et al. *Condensed heterocyclic compounds: Synthesis and antiinflammatory activity of novel thiazolo[3,2-a]pyrimidines*. Arch Pharm 1998, 331(6): 201.

CDB

266609

2-[2-Methyl-3,5-(diphenyl)phenyl]acetic acid



C21 H18 O2; Mol wt: 302.3712

ACTION – Antiinflammatory/analgesic agent, an arylacetic acid whose mechanism of action appears to involve inhibition of cyclooxygenase type 1 (COX-1). It dose-dependently inhibited carrageenan-induced edema in rats (ED₅₀ = 41 mg/kg s.c. at 3 h) for up to 12 h, but had no effect against bradykinin- or 5-HT-induced edema in these animals. Significant analgesic activity was observed in the phenylquinone writhing test in mice (70% inhibition at 50 mg/kg s.c.), and it was also active in rats with adjuvant-induced arthritis (> 70% inhibition of hind paw inflammation at 100 mg/kg/day s.c. starting on day 13). The compound significantly inhibited COX-1 (IC₅₀ approx. 17 μ M), whereas it was much less active against COX-2 (IC₅₀ approx.120 μ M) and had negligible activity against peptidylglycine α -monooxygenase (IC₅₀ approx. 550 μ M). Further modifications to this molecule may lead to potent antiinflammatory agents with greater inhibitory activity on COX-2.

SOURCES – University of Georgia, Athens (US); Georgia Inst. Technol., Atlanta (US); Mercer University, Atlanta (US).

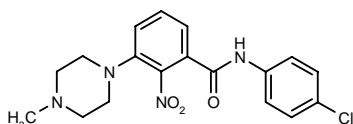
REFERENCES

1. Cutler, S.J. et al. *Pharmacological evaluation of 1-(carboxymethyl)-3,5-diphenyl-2-methylbenzene, a novel arylacetic acid with potential anti-inflammatory properties.* Inflamm Res 1998, 47(7): 316.

DU-6712*

251591

N-(4-Chlorophenyl)-3-(4-methylpiperazin-1-yl)-2-nitrobenzamide



C18 H19 Cl N4 O3; Mol wt: 374.8261

ACTION – Antiinflammatory and immunomodulating agent, a benzamide structurally related to LF-1695 that also appears to have bone-sparing effects. In addition to preventing the development of chronic paw edema in an adjuvant-induced arthritis model in rats at doses of 5, 15 and 45 mg/kg/day p.o. for 28 days, it also alleviated the reductions in bone minerals, bone strength and trabecular bone formation and the increase in osteoclast number in these animals, indicating its ability to improve bone turnover.

SOURCE – Daiichi Pharmaceutical.

REFERENCES

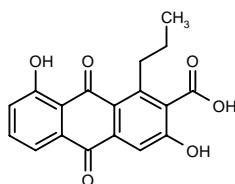
1. Kawagoe, K. et al. (Daiichi Pharmaceutical Co., Ltd.) *Benzamide cpds.* JP 97059236.
2. Kawagoe, K. et al. *Antirheumatics: Synthesis and structure-activity relationships of 1,2,3-substituted benzamides.* AFMC Int Med Chem Symp (Sept 3-8, Tokyo) 1995, Abst P13M183.
3. Uchiyama, Y. et al. *Modulation of bone mass, strength, and turnover by a new benzamide compound, DU-6712, in adjuvant-induced arthritic rats.* Calcif Tissue Int 1998, 62(6): 519.

*Identified compound **251591** (see **250965**) Drug Data Report 1997, 019(08): 0735.

K-1115A

265577

3,8-Dihydroxy-1-propyl-9,10-anthraquinone-2-carboxylic acid



C18 H14 O6; Mol wt: 326.3026

Orange rods, *m.p.* 255-8 °C.

ACTION – Anthraquinone inhibitor of activator protein-1 (AP-1) isolated from the culture broth of *Streptomyces griseorubiginosus* Mer-K1115; it inhibited the direct binding of AP-1 to AP-1 oligonucleotide with an IC₅₀ value of 100 μM, and the production of collagenase in IL-1α-stimulated rat synovial cells (IC₅₀ = 60 μM). Topically administered K-1115A concentration-dependently (40-99% at 3-10 μmol/200 μl) attenuated the inflammatory response mediated by AP-1 in the phorbol myristate acetate (PMA)-induced ornithine decarboxylase (ODC) activation model in mice. Potentially useful as an antiinflammatory agent for the treatment of rheumatoid arthritis, as well as for transplant rejection and tumors.

SOURCES – Eisai; Mercian.

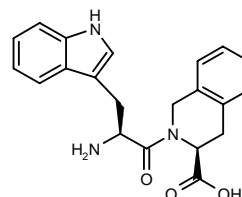
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1. Goto, M. et al. *K1115 A, a new anthraquinone derivative that inhibits the binding of activator protein-1 (AP-1) to its recognition sites. I. Biological activities.* J Antibiot 1998, 51(6): 539.
2. Naruse, N. et al. *K1115 A, a new anthraquinone derivative that inhibits the binding of activator protein-1 (AP-1) to its recognition sites. II. Taxonomy, fermentation, isolation, physico-chemical properties and structure determination.* J Antibiot 1998, 51(6): 545.

TSL-225

265601

L-Tryptophyl-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxylic acid



C21 H21 N3 O3; Mol wt: 363.4149

ACTION – Potent dipeptide inhibitor of dipeptidyl peptidase IV (DPP IV; IC₅₀ = 5.7 μM).

Inhibitors of DPP IV have been shown to block the proliferative response of T-cells to antigenic stimulation and to suppress IL-2 production, and such compounds are therefore expected to have therapeutic potential in the treatment of autoimmune diseases such as rheumatoid arthritis.

SOURCE – Tanabe Seiyaku.

REFERENCES

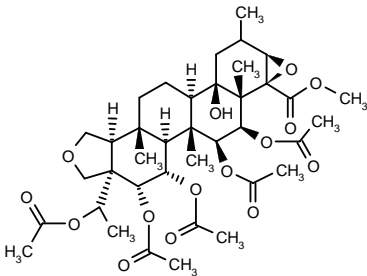
1. Sugita, T. et al. (Tanabe Seiyaku Co., Ltd.) *Tetrahydroisoquinoline derivs.* JP 98182613, WO 9818763.
2. Yamada, M. et al. *A potent dipeptide inhibitor of dipeptidyl peptidase IV.* Bioorg Med Chem Lett 1998, 8(12): 1537.

IMMUNOMODULATING AGENTS

IMMUNOSUPPRESSANTS

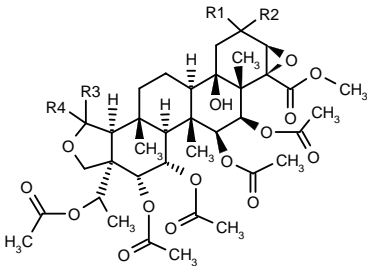
264849

(3aα,4α,5α,5aα,5bβ,6β,7β,7aβ,8β,9β,11aβ,11bα,13aβ,13bα)-4,5,6,7-Tetraacetoxy-3a-(1-acetoxyethyl)-8,9-epoxy-11a-hydroxy-5b,7a,10,13a-tetramethylperhydrochryseno[1,2-c]furan-8-carboxylic acid methyl ester



C38 H54 O15; Mol wt: 750.8296

ACTION – Immunosuppressive agent that acts by inhibiting voltage-dependent potassium Kv1.3 channels present on human T-lymphocytes (IC₅₀ < 10 μM), reported to be associated with few side effects. A representative compound from a series of specifically claimed triterpene derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
266263	Me	H	-O-		C ₃₈ H ₅₂ O ₁₆
266264		-O-	H	H	C ₃₇ H ₅₀ O ₁₆
266265	OCH ₂ OMe	H	H	H	C ₃₉ H ₅₆ O ₁₇
266266	OCH ₂ OEt	H	H	H	C ₄₀ H ₅₈ O ₁₇
266267	OCH ₂ OC ₈ H ₁₇	H	H	H	C ₄₆ H ₇₀ O ₁₇
266284	OCH ₂ OCH ₂ Ph	H	H	H	C ₄₅ H ₆₀ O ₁₇
266285	OEt	H	H	H	C ₃₉ H ₅₆ O ₁₆

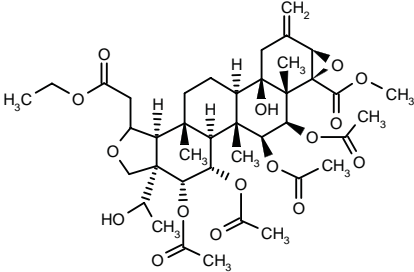
SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Triterpene derivs. with immunosuppressant activity*. WO 9816531.

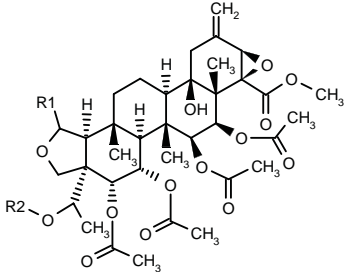
264850

(3aα,4α,5α,5aα,5bβ,6β,7β,7aβ,8β,9β,11aβ,11bα,13aβ,13bα)-4,5,6,7-Tetraacetoxy-8,9-epoxy-1-(ethoxycarbonylmethyl)-11a-hydroxy-3a-(1-hydroxymethyl)-5b,7a,13a-trimethyl-10-methyleneperhydrochryseno[1,2-c]furan-8-carboxylic acid methyl ester



C40 H56 O16; Mol wt: 792.8664

ACTION – Immunosuppressive agent that acts by inhibiting the voltage-dependent Kv1.3 potassium channel present on human T-lymphocytes (IC₅₀ < 10 μM) and is reported to have few side effects. A representative compound from a series of specifically claimed triterpene derivatives, wherein the following are also included:



Compound	R1	R2	Formula
267125	CH ₂ CO ₂ Me	H	C ₃₉ H ₅₄ O ₁₆
267126	CH ₂ CH ₂ OH	Ac	C ₄₀ H ₅₆ O ₁₆
267127	vinyl	Ac	C ₄₀ H ₅₄ O ₁₅
267128	CH ₂ CONHCH ₂ Ph	Ac	C ₄₇ H ₆₁ NO ₁₆

SOURCE – Merck & Co.

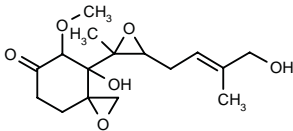
REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Triterpene derivs. with immunosuppressant activity*. WO 9816532.

AM-6927

265250

4-(1,2-Epoxy-6-hydroxy-1,5-dimethyl-4-hexenyl)-4-hydroxy-5-methoxy-1-oxaspiro[2.5]octan-6-one



C16 H24 O6; Mol wt: 312.3596

ACTION – Immunosuppressive agent isolated from *Metarhizium anisopliae* var. *anisopliae* M6927 (FERM P-15942), proven to inhibit IgE production in spleen cells of sensitized mice stimulated with lipopolysaccharide (LPS) and IL-4 ($IC_{50} = 0.0007 \mu\text{g/ml}$), without cytotoxicity ($IC_{50} > 50 \mu\text{g/ml}$ against P388D1 cells).

SOURCE – Asahi Chemical.

REFERENCES

1. Ishikawa, S. and Yokoi, H. (Asahi Chemical Industry Co., Ltd.) *Novel cpd. AM6927 and its preparation method.* JP 98139771.

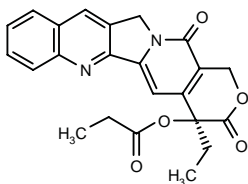
ONCOLYTIC DRUGS

DNA-INTERCALATING DRUGS

261782

4(S)-Ethyl-4-(propionyloxy)-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione

20(S)-(Propionyloxy)camptothecin



C23 H20 N2 O5; Mol wt: 404.4200

ACTION – Camptothecin ester whose lactone form shows a significantly increased biological life span in both human and mouse plasma compared to the lactone form of camptothecin. It inhibited the proliferation of human leukemia cells and induced cell death. *In vivo*, compound demonstrated significant activity against human breast carcinoma CLO and human lung carcinoma SPA in nude mice, with much lower toxicity compared to camptothecin.

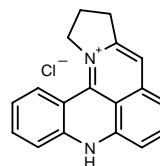
SOURCE – Stehlin Found. Cancer Res., Houston, TX (US).

REFERENCES

1. Zhisong, C. and Ciovanella, B.C. (The Stehlin Foundation for Cancer Research) *Derivs. of camptothecin for use in treating cancer.* WO 9728165.
2. Cao, Z. et al. *Alkyl esters of camptothecin and 9-nitrocamptothecin: Synthesis, in vitro pharmacokinetics, toxicity, and antitumor activity.* J Med Chem 1998, 41(1): 31.
3. Cao, Z. et al. *Alkyl esters of camptothecin: Synthesis, toxicity and antitumor activity.* Proc Amer Assoc Cancer Res 1998, Abst 2858.

265019

1,2,3,8-Tetrahydroindolizino[7,6,5-k]acridinium chloride



C18 H15 Cl N2; Mol wt: 294.7835

ACTION – Water-soluble DNA-binding antineoplastic agent that is a potent inducer of apoptosis in lung and breast cancer cell lines, with a mean GI_{50} value of $< 0.1 \mu\text{M}$. It shows selectivity for melanoma cell lines at the LC_{50} level and was active *in vivo* in mice bearing murine MAC15A tumors. Considered a promising clinical candidate.

SOURCES – Univ. Bradford, Bradford (GB); Univ. Nottingham, Nottingham (GB).

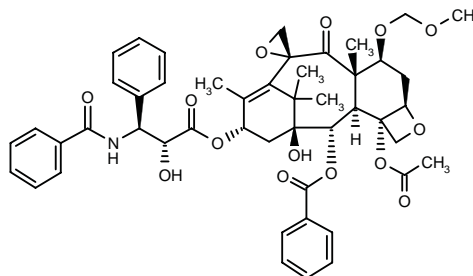
REFERENCES

1. Hagan, D.J. et al. *New DNA interactive aza-polycyclic compounds: Physical and biological properties.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 135.

ANTIMITOTIC DRUGS

264399

[2aR-[2a α ,4 β ,4a β ,6S,9 α (2R,3S),11 β ,12 α ,12a α ,12b α]]-12b-Acetoxy-9-(3-benzamido-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-11-hydroxy-4-(methoxymethoxy)-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-spiro[7,11-methanocyclodeca[3,4]benz[1,2-b]oxete-6,2'-oxiran]-5-one



C48 H53 N O14; Mol wt: 867.9397

ACTION – Antineoplastic agent, a paclitaxel analog with comparable *in vitro* cytotoxicity against human colon tumor HCT116 cells ($IC_{50} = 1.5 \text{ nM}$ vs. 1.0 nM for paclitaxel). Another compound from this series of C-10 epoxy taxanes is:

ACTION – Immunosuppressive agent isolated from *Metarhizium anisopliae* var. *anisopliae* M6927 (FERM P-15942), proven to inhibit IgE production in spleen cells of sensitized mice stimulated with lipopolysaccharide (LPS) and IL-4 ($IC_{50} = 0.0007 \mu\text{g/ml}$), without cytotoxicity ($IC_{50} > 50 \mu\text{g/ml}$ against P388D1 cells).

SOURCE – Asahi Chemical.

REFERENCES

1. Ishikawa, S. and Yokoi, H. (Asahi Chemical Industry Co., Ltd.) *Novel cpd. AM6927 and its preparation method.* JP 98139771.

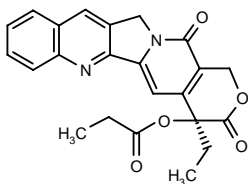
ONCOLYTIC DRUGS

DNA-INTERCALATING DRUGS

261782

4(S)-Ethyl-4-(propionyloxy)-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-dione

20(S)-(Propionyloxy)camptothecin



C23 H20 N2 O5; Mol wt: 404.4200

ACTION – Camptothecin ester whose lactone form shows a significantly increased biological life span in both human and mouse plasma compared to the lactone form of camptothecin. It inhibited the proliferation of human leukemia cells and induced cell death. *In vivo*, compound demonstrated significant activity against human breast carcinoma CLO and human lung carcinoma SPA in nude mice, with much lower toxicity compared to camptothecin.

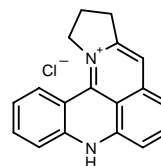
SOURCE – Stehlin Found. Cancer Res., Houston, TX (US).

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2. Cao, Z. et al. *Alkyl esters of camptothecin and 9-nitrocamptothecin: Synthesis, in vitro pharmacokinetics, toxicity, and antitumor activity.* J Med Chem 1998, 41(1): 31.
3. Cao, Z. et al. *Alkyl esters of camptothecin: Synthesis, toxicity and antitumor activity.* Proc Amer Assoc Cancer Res 1998, Abst 2858.

265019

1,2,3,8-Tetrahydroindolizino[7,6,5-k]acridinium chloride



C18 H15 Cl N2; Mol wt: 294.7835

ACTION – Water-soluble DNA-binding antineoplastic agent that is a potent inducer of apoptosis in lung and breast cancer cell lines, with a mean GI_{50} value of $< 0.1 \mu\text{M}$. It shows selectivity for melanoma cell lines at the LC_{50} level and was active *in vivo* in mice bearing murine MAC15A tumors. Considered a promising clinical candidate.

SOURCES – Univ. Bradford, Bradford (GB); Univ. Nottingham, Nottingham (GB).

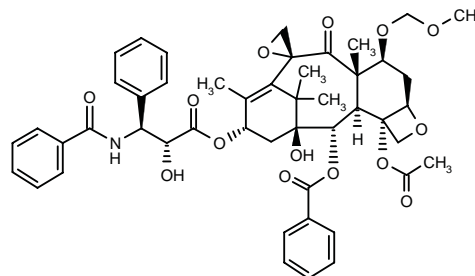
REFERENCES

1. Hagan, D.J. et al. *New DNA interactive aza-polycyclic compounds: Physical and biological properties.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 135.

ANTIMITOTIC DRUGS

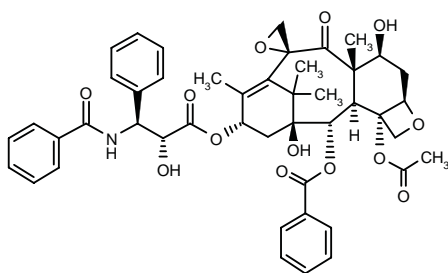
264399

[2aR-[2a α ,4 β ,4a β ,6S,9 α (2R,3S),11 β ,12 α ,12a α ,12b α]]-12b-Acetoxy-9-(3-benzamido-2-hydroxy-3-phenylpropionyloxy)-12-benzoyloxy-11-hydroxy-4-(methoxymethoxy)-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-spiro[7,11-methanocyclodeca[3,4]benz[1,2-b]oxete-6,2'-oxiran]-5-one



C48 H53 N O14; Mol wt: 867.9397

ACTION – Antineoplastic agent, a paclitaxel analog with comparable *in vitro* cytotoxicity against human colon tumor HCT116 cells ($IC_{50} = 1.5 \text{ nM}$ vs. 1.0 nM for paclitaxel). Another compound from this series of C-10 epoxy taxanes is:



266026: C₄₆ H₄₉ N O₁₃

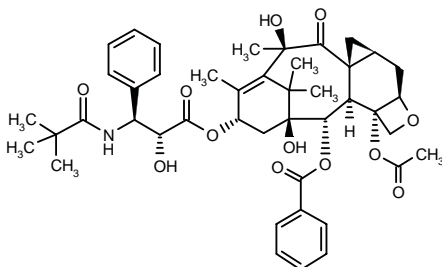
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Walker, M.A. and Kadow, J.F. (Bristol-Myers Squibb Co.) *C-10 epoxy taxanes*. US 5773468, WO 9814187.

265875

[1*S*-(1 α ,2 β ,4 α ,7 β ,8 α *R*,9 $\alpha\alpha$,10 $\alpha\alpha$,12 $\alpha\alpha$,12 $\beta\alpha$)]-12a-Acetoxy-1-benzoyloxy-4-[3(*S*)-(tert-butoxycarbonylamino)-2(*R*)-hydroxy-3-phenylpropionyloxy]-2,7-dihydroxy-2,5,7,13,13-pentamethyl-2,3,4,7,8,9,9a,10,10a,12,12a,12b-dodecahydro-2,6-methanocyclodeca[3,4]cyclopropa[4,5]benz[1,2-*b*]oxet-8-one



C₄₄ H₅₃ N O₁₂; Mol wt: 787.8977

ACTION – Antineoplastic agent, a taxane derivative reported to be at least as active as paclitaxel and docetaxel in a tubulin polymerization assay. *In vivo*, compound is reported to be active in mice bearing B16 melanoma tumors at doses of between 1 and 10 mg/kg i.p.

SOURCE – Rhône-Poulenc Rorer.

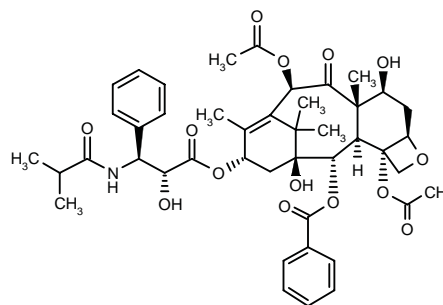
REFERENCES

1. Bouchard, H. et al. (Rhône-Poulenc Rorer SA) *Taxoids, their preparation and pharmaceutical compsns. containing them*. US 5777139, WO 9533737.

CANADENSOL

264883

[2*aR*-[2 $\alpha\alpha$,4 β ,4 $\alpha\beta$,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12 $\alpha\alpha$,12 $\beta\alpha$]]-6,12b-Diacetoxy-12-benzoyloxy-4,11-dihydroxy-9-(3-isobutyramido-2-hydroxy-3-phenylpropionyloxy)-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz-[1,2-*b*]oxet-5-one



C₄₄ H₅₃ N O₁₄; Mol wt: 819.8957

ACTION – Antineoplastic agent, a taxane isolated from the Canadian yew *Taxus canadensis*, with more potent antimitotic activity than paclitaxel, as demonstrated in a microtubule assay. Compound was found to be as active as paclitaxel in inhibiting the growth of human ovarian carcinoma A2780 cells (IC₅₀ = 21.32 and 16.96 nM, respectively). *In vivo*, it was shown to inhibit the growth of paclitaxel-resistant murine mammary adenocarcinoma DA3 implanted in mice at 40 mg/kg i.v. x 2, without toxic effects.

SOURCE – BioChem Pharma.

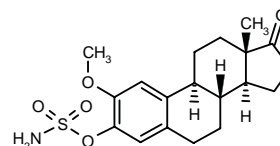
REFERENCES

1. Zamir, L. et al. (BioChem Pharma Inc.) *A family of canadensol taxanes, the semi-synthetic preparation and therapeutic use thereof*. WO 9817656.

HORMONAL AGENTS

265414

3-(Aminosulfonyloxy)-2-methoxyestra-1,3,5(10)-trien-17-one



C₁₉ H₂₅ N O₅ S; Mol wt: 379.4745

ACTION – Potent steroid sulfatase inhibitor, as demonstrated both *in vitro* and *in vivo*, devoid of estrogenicity, potentially useful in the treatment of breast cancer.

SOURCES – University of Bath, Bath (GB); Imperial Coll. School Med., London (GB).

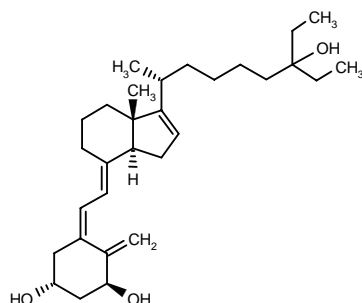
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1. Purohit, A. et al. *The development of A-ring modified analogues of oestrone-3-O-sulphamate as potent steroid sulphatase inhibitors with reduced oestrogenicity.* J Steroid Biochem Mol Biol 1998, 64(5-6): 269.

2. Reed, M.J. et al. *Steroid sulphatase inhibitors.* 10th Int Cong Horm Steroids (June 17-21, Quebec) 1998, 52.

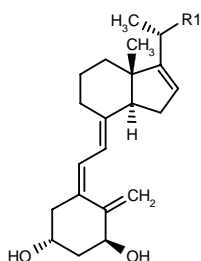
266211

(1*S*,3*R*,20*R*)-20-(5-Ethyl-5-hydroxyheptyl)-9,10-secopregna-5(*Z*),7(*E*),10(19),16-tetraene-1,3-diol



C30 H48 O3; Mol wt: 456.7062

ACTION – Vitamin D₃ analog with antiproliferative, immunosuppressive and antiinflammatory activity. Compound was found to exhibit 43-fold more potent antiproliferative properties in HaCaT cells and 5-fold more potent immunosuppressive activity in the mixed lymphocyte reaction (MLR) assay than 1 α ,25-dihydroxyvitamin D₃, while showing about 2-fold lower calcemic activity. Claimed for the treatment or prevention of hyperparathyroidism, diseases characterized by abnormal cell differentiation and/or proliferation such as cancer, psoriasis and myelofibrosis, as well as other diseases states such as diabetes mellitus, hypertension, acne, alopecia, skin aging, AIDS, neurodegenerative disorders, graft-vs.-host reaction, transplant rejection, inflammatory diseases and osteoporosis. Other specifically claimed vitamin D analogs include the following:



Compound	R1	Formula
267241	3-[C(Me)2OH]-PhSCH2	C ₃₁ H ₄₂ O ₃ S
267243	3-[C(Me)2OH]-PhOCH2	C ₃₁ H ₄₂ O ₄
267244	(<i>E,E</i>)-CH=CHCH=CHC(Et)2OH	C ₃₀ H ₄₄ O ₃
267245	(<i>E</i>)-cyclopropyl-CH(OH)CH=CH	C ₂₇ H ₃₈ O ₃

SOURCE – Leo Denmark.

REFERENCES

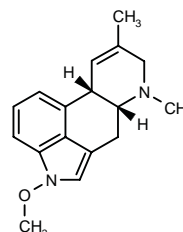
1. Von Daehne, W. (Leo Pharmaceutical Products Ltd. A/S) *Vitamin D3 derivs.* WO 9824762.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

262245

(6*aR*,10*aS*)-4-Methoxy-7,9-dimethyl-4,6,6*a*,7,8,10*a*-hexahydroindolo[4,3-*fg*]quinoline

(5*R*,10*S*)-1-Methoxyagroclavine



C17 H20 N2 O; Mol wt: 268.3580

$[\alpha]_D -63^\circ$ (*c* 0.08, MeOH).

ACTION – Selective inhibitor of p56^{lck} tyrosine kinase produced by the fermentation of *Penicillium* sp. WC75209, identified as a new member of the ergot alkaloid family. It inhibited the autophosphorylation of p56^{lck} tyrosine kinase with an IC₅₀ of 8.5 μ M, whereas it was much less active against p75^{blk} (IC₅₀ = 285.0 μ M) and exerted little or no effect against other protein kinases. The compound was not cytotoxic to mouse lung carcinoma M109 cells at concentrations up to 40 μ M.

p56^{lck}, p59^{lyn}, ZAP-70 and p72^{syk} tyrosine kinases have been implicated in T-cell activation and inhibitors of these enzymes are suggested to be useful as inhibitors of T-cell activation.

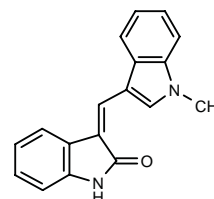
SOURCE – Bristol-Myers Squibb.

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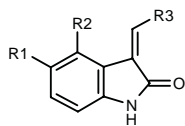
263291

(*Z*)-3-(1-Methylindol-3-ylmethylene)indolin-2-one



C18 H14 N2 O; Mol wt: 274.3216

ACTION – A specific inhibitor of FLK protein kinase (IC₅₀ = 0.7 μ M) with potential in the treatment or prevention of disorders related to unregulated protein kinase signal transduction including cell proliferative diseases such as cancer, atherosclerosis, arthritis and restenosis, and metabolic disorders such as diabetes. Other water-soluble indolinone compounds include the following:



Compound	R1	R2	R3	Isomer	Formula
265797	Me	H	1-Me-3-indolyl	Z	C ₁₉ H ₁₆ N ₂ O
265798	H	NH2	1-Me-3-indolyl	Z	C ₁₈ H ₁₅ N ₃ O
265799	H	F	1-Me-3-indolyl	Z	C ₁₈ H ₁₃ FN ₂ O
265800	H	H	5-MeO-3-indolyl	Z	C ₁₈ H ₁₄ N ₂ O ₂
265801	H	NH2	4,5,6,7-tetrahydro-2-indolyl	Z	C ₁₇ H ₁₇ N ₃ O
265802	H	H	4,5,6,7-tetrahydro-2-indolyl	Z	C ₁₇ H ₁₆ N ₂ O
265803	H	Cl	4,5,6,7-tetrahydro-2-indolyl	Z	C ₁₇ H ₁₅ ClN ₂ O
265804	H	H	4,5,6,7-tetrahydro-2-indolyl	E	C ₁₇ H ₁₆ N ₂ O
265805	H	Br	4,5,6,7-tetrahydro-2-indolyl	E	C ₁₇ H ₁₅ BrN ₂ O
265806	H	Cl	2-pyrrolyl	Z	C ₁₃ H ₉ ClN ₂ O
265807	H	H	2-pyrrolyl	Z	C ₁₃ H ₁₀ N ₂ O
265808	H	NH2	3,4-(Br)-5-Me-2-pyrrolyl	Z	C ₁₄ H ₁₁ Br ₂ N ₃ O

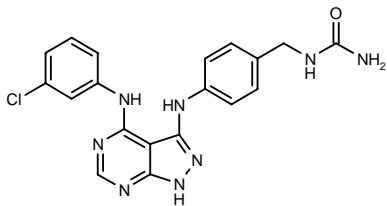
SOURCE – Sugen.

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1. Tang, P.C. et al. (Sugen, Inc.) *Indolinone combinatorial libraries and related products and methods for the treatment of disease.* WO 9807695.

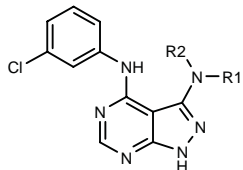
264415

N-[4-[4-(3-Chlorophenylamino)-1H-pyrazolo[3,4-d]pyrimidin-3-ylamino]benzyl]urea



C19 H17 Cl N8 O; Mol wt: 408.8513

ACTION – Antineoplastic agent that inhibits epidermal growth factor (EGF) receptor tyrosine kinase, as well as other tyrosine kinases involved in growth factor-mediated signal transduction such as abl kinase, c-src kinase and c-erbB2 kinase, and also serine/threonine kinases such as protein kinase C. Other specifically claimed compounds from this series of 4-amino-1H-pyrazolo[3,4-d]pyrimidines are:



Compound	R1	R2	Formula
265024	H	3-Pyr	C ₁₆ H ₁₂ ClN ₇
265025	Me	4-Pyr	C ₁₇ H ₁₄ ClN ₇

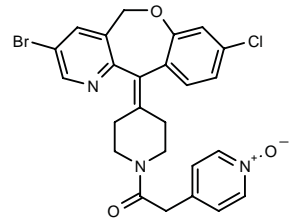
SOURCE – Novartis.

REFERENCES

1. Bold, G. et al. (Novartis AG) *Pyrimidines derivs. and processes for the preparation thereof.* WO 9814450.

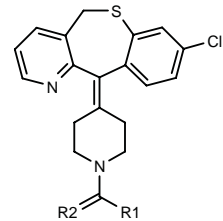
264441

3-Bromo-8-chloro-11-[1-[2-(1-oxidopyridin-4-yl)acetyl]-piperidin-4-ylidene]-5,11-dihydro[1]benzoxepine[4,3-b]-pyridine

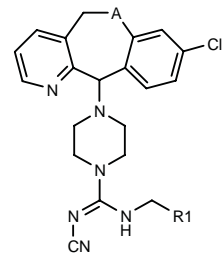


C25 H21 Br Cl N3 O3; Mol wt: 526.8159

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and of the farnesylation of the oncogene protein Ras. Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	Formula
266958	4-Pyr-CH2	O	C ₂₅ H ₂₂ ClN ₃ OS
266960	4-Pyr-CH2NH	N(CN)	C ₂₆ H ₂₃ ClN ₆ S
266961	1-oxido-3-Pyr-CH2NH	N(CN)	C ₂₆ H ₂₃ ClN ₆ OS



Compound	R1	A	Formula
266959	4-Pyr	S	C ₂₅ H ₂₄ ClN ₇ S
266962	1-oxido-3-Pyr	S	C ₂₅ H ₂₄ ClN ₇ OS
266963	4-Pyr	N(Me)	C ₂₆ H ₂₇ ClN ₈

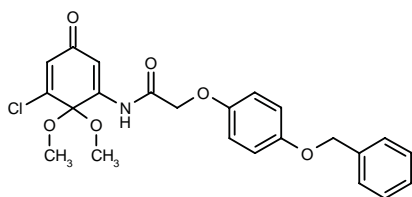
SOURCE – Schering-Plough.

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1. Afonso, A. et al. (Schering Corp.) *Tricyclic cpds. having activity as Ras-FPT inhibitors.* WO 9815556.

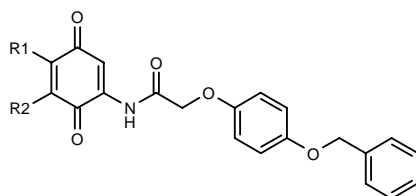
264871

2-(4-Benzyloxyphenoxy)-*N*-(5-chloro-6,6-dimethoxy-3-oxocyclohexa-1,4-dienyl)acetamide



C23 H22 Cl N O6; Mol wt: 443.8808

ACTION – Antineoplastic agent, a protein farnesyltransferase inhibitor (48% inhibition at 11.1 μ M) proven to inhibit the proliferation of v-H-*ras*-transformed 3Y1-B (HR-3Y1) cells with an IC_{50} value of 0.14 μ M. Other compounds from this series of 1,4-benzoquinone derivatives include the following:



Compound	R1	R2	Formula
266096	OCH ₂ CH ₂ OCH ₂ CH ₂ OMe	H	C ₂₆ H ₂₇ NO ₈
266097	OCH ₂ CH ₂ OCH ₂ CH ₂ -OCH ₂ CH ₂ OH	H	C ₂₇ H ₂₉ NO ₉
266098	SCH ₂ CO ₂ Et	H	C ₂₆ H ₂₃ NO ₇ S
266099	SCH ₂ CO ₂ Et	SCH ₂ CO ₂ Et	C ₂₉ H ₂₉ NO ₉ S ₂
266100	SCH ₂ CO ₂ Et	Cl	C ₂₆ H ₂₂ ClNO ₇ S
266101	4-(AcNH)-PhS	H	C ₂₉ H ₂₄ N ₂ O ₆ S
266102	4-Br-PhS	H	C ₂₇ H ₂₀ BrNO ₅ S

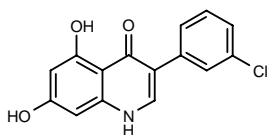
SOURCE – Kyowa Hakko.

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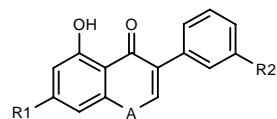
264886

3-(3-Chlorophenyl)-5,7-dihydroxyquinolin-4(1*H*)-one



C15 H10 Cl N O3; Mol wt: 287.7010

ACTION – Agent for the treatment of proliferative diseases such as cancer and psoriasis, an inhibitor of protein kinases such as epidermal growth factor (EGF) receptor protein tyrosine kinase (IC_{50} = 0.008 μ M). Antiproliferative activity was demonstrated by inhibition of the growth of mouse epidermoid keratinocytes (IC_{50} = 10.2 mcM). Within this series of specifically claimed phenyl-substituted bicyclic heterocyclyl derivatives, the following are also included:



Compound	R1	R2	A	Formula
265766	OH	Cl	O	C ₁₅ H ₉ ClO ₄
265767	OMe	Cl	O	C ₁₆ H ₁₁ ClO ₄
265768	OMe	Cl	NH	C ₁₆ H ₁₂ ClNO ₃
265769	OMe	Cl	N(Me)	C ₁₇ H ₁₄ ClNO ₃
265770	OMe	Cl	N(CH ₂ CH ₂ Ph)	C ₂₄ H ₂₀ ClNO ₃
265771	OMe	Cl	N(CH ₂ CO ₂ Me)	C ₁₉ H ₁₆ ClNO ₅

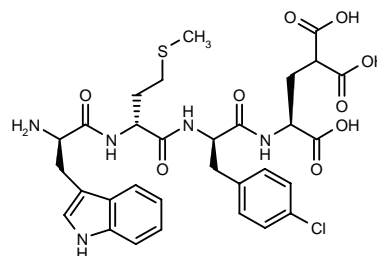
SOURCE – Novartis.

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1. Traxler, P. et al. (Novartis AG) *Phenyl-substd. bicyclic heterocyclyl derivs. and their use.* WO 9817662.

265014

D-Tryptophyl-D-methionyl-D-(4-chloro)phenylalanyl-L-(γ -carboxy)glutamic acid



C31 H36 Cl N5 O9 S; Mol wt: 690.1704

ACTION – The most potent inhibitor of protein farnesyltransferase (IC_{50} = 1.3 nM) from a series of tetrapeptides; it is noncompetitive with the substrate *ras* but rather induces the same conformational change in the enzyme as the cosubstrate farnesyl diphosphate. Suggested to represent a promising lead for the development of a new class of inhibitors.

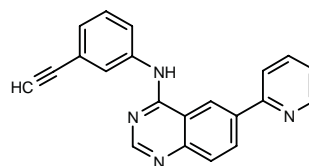
SOURCE – Merck & Co.

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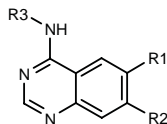
265143

N-(3-Ethynylphenyl)-*N*-[6-(2-pyridyl)quinazolin-4-yl]amine



C21 H14 N4; Mol wt: 322.3696

ACTION – Antineoplastic agent that inhibits abnormal cell growth by blocking overexpression of epidermal growth factor (EGF) receptor tyrosine kinase. Potentially useful in the treatment or prevention of hyperproliferative disorders such as cancer, psoriasis and benign prostatic hyperplasia. Within this series of specifically claimed 4-aminoquinazoline derivatives, the following are also included:



Compound	R1	R2	R3	Formula
267119	3-Pyr	H	3-(ethynyl)-Ph	C ₂₁ H ₁₄ N ₄
267120	3-Pyr	H	5-indolyl	C ₂₁ H ₁₅ N ₅
267121	4-Pyr-CH=CH	H	3-(ethynyl)-Ph	C ₂₃ H ₁₆ N ₄
267122	4-Pyr-CH=CH	H	5-indolyl	C ₂₃ H ₁₇ N ₅
267123	4-Pyr-CH=CH	OMe	5-indolyl	C ₂₄ H ₁₉ N ₅ O
267124	4-Pyr-CH=CH	H	3-(5-oxazolyl)-Ph	C ₂₄ H ₁₇ N ₅ O

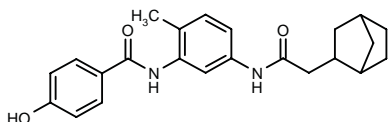
SOURCE – Pfizer.

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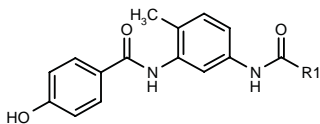
265502

N-[5-[2-(Bicyclo[2.2.1]heptan-2-yl)acetamido]-2-methylphenyl]-4-hydroxybenzamide



C₂₃ H₂₆ N₂ O₃; Mol wt: 378.4694

ACTION – Antineoplastic agent that acts by inhibiting raf kinase and is particularly suited for the treatment of tumors with a high incidence of *ras* mutation such as colon, lung and pancreatic tumors. Other compounds from this series of benzamide derivatives are:



Compound	R1	Formula
266669	3,4-(Cl)2-PhCH ₂	C ₂₂ H ₁₈ Cl ₂ N ₂ O ₃
266670	3-N(Me)2-Ph	C ₂₃ H ₂₃ N ₃ O ₃

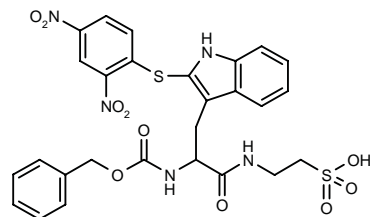
SOURCE – Zeneca.

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265872

2-[2-(Benzyloxycarbonylamino)-3-[2-(2,4-dinitrophenyl-sulfanyl)-1*H*-indol-3-yl]propionamido]ethanesulfonic acid



C₂₇ H₂₅ N₅ O₁₀ S₂; Mol wt: 643.6515

ACTION – Antineoplastic agent, an inhibitor of insulin receptor tyrosine kinase (InsRTK) and other related protein tyrosine kinases, reported to be cell-permeable by virtue of its hydrophobic nature. Compound was found to inhibit InsRTK-mediated PolyGlu₄Tyr phosphorylation (IC₅₀ = 130 μM), as well as insulin- or vanadate-stimulated lipogenesis in rat adipocytes (IC₅₀ = 170 and 45 μM, respectively). Selectivity for tyrosine kinases was shown by negligible inhibition of isoproterenol-mediated lipolysis in rat adipocytes. Compound was also found to inhibit the insulin-dependent proliferation of murine lymphoid T-cell LB3 leukemia cells with an IC₅₀ value of 0.95 μM, which is about 200-fold lower than the concentration required to inhibit the normal metabolic biological effects of insulin.

SOURCES – Yeda; Yissum.

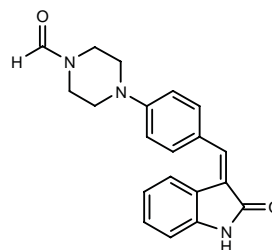
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SU-4984

266048

(*E*)-4-[4-(2-Oxindolin-3-ylidenemethyl)phenyl]piperazine-1-carbaldehyde



C₂₀ H₁₉ N₃ O₂; Mol wt: 333.3891

Yellow solid.

ACTION – Protein tyrosine kinase inhibitor proven to inhibit the kinase activity of fibroblast growth factor (FGF) receptor FGFR1 using purified enzyme (IC₅₀ = 10-20 μM) and FGFR1 autophosphorylation induced by acidic FGF (aFGF) in NIH 3T3 cells (IC₅₀ = 20-40 μM); it also inhibited aFGF-induced tyrosine phosphorylation of the mitogen-activated protein (MAP) kinases ERK1 and ERK2 (events dependent on FGFR1 kinase activity) and aFGF-induced [³H]-thymidine incorporation in NIH 3T3 cells. SU-4984 was also found to inhibit tyrosine phosphorylation of the platelet-derived growth factor (PDGF) receptor and the insulin receptor in NIH 3T3 cells, but it did not inhibit the kinase activity of the epidermal growth factor (EGF) receptor.

SU-4984 exists predominantly in the *E* form but is isomerized to the *Z* form before or during the interaction with the enzyme.

SOURCE – Sugen.

REFERENCES

1. Mohammadi, M. et al. (Sugen, Inc.) *Crystal structures of a protein tyrosine kinase*. WO 9807835.

2. Tang, P.C. et al. (Sugen, Inc.) *Indolinone combinatorial libraries and related products and methods for the treatment of disease*. WO 9807695.

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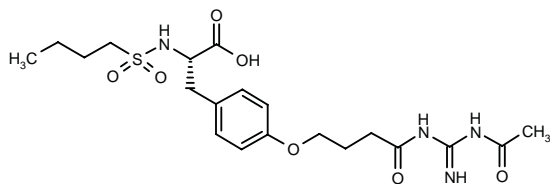
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5. Sun, L. et al. *Synthesis and biological evaluations of 3-substituted indolin-2-ones: A novel class of tyrosine kinase inhibitors that exhibit selectivity toward particular receptor tyrosine kinases*. J Med Chem 1998, 41(14): 2588.

ANTIANGIOGENIC AGENTS

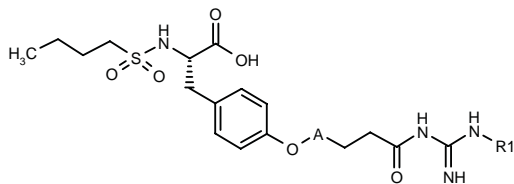
261153

4-*O*-[4-(*N*³-Acetylguanidino)-4-oxobutoxy]-*N*-(butylsulfonyl)-L-tyrosine



C20 H30 N4 O7 S; Mol wt: 470.5440

ACTION – An inhibitor of αv integrins, particularly αvβ3 (vitronectin receptor; IC₅₀ = 6.5 nM) and αvβ5 (IC₅₀ = 55 nM), with much lower affinity for the fibrinogen (gpIIb/IIIa) receptor (IC₅₀ = 1860 nM). Potentially useful for the treatment of cardiovascular disorders such as thrombosis, arteriosclerosis, myocardial infarction and coronary heart disease, osteoporosis and disorders characterized by angiogenesis such as tumors. Other specifically claimed compounds from this series of phenylalanine derivatives include the following:



Compound	R1	A	Formula
266453	H	CH2	C ₁₈ H ₂₈ N ₄ O ₆ S
266458	Et	(CH2)2	C ₂₁ H ₃₄ N ₄ O ₆ S
266459	H	(CH2)2	C ₁₉ H ₃₀ N ₄ O ₆ S

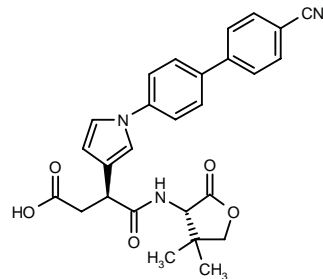
SOURCE – Merck KGaA.

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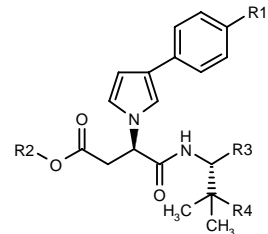
264873

3(*S*)-[1-(4'-Cyanobiphenyl-4-yl)pyrrol-3-yl]-*N*-[4,4-dimethyl-2-oxotetrahydrofuran-3(*S*)-yl]succinamic acid

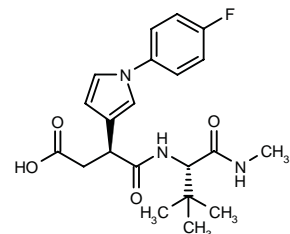


C27 H25 N3 O5; Mol wt: 471.5105

ACTION – An inhibitor of matrix metalloproteinases such as human stromelysin and gelatinase A, with favorable pharmacokinetics in rats following oral dosing. Claimed for the treatment of tumor growth, invasion and metastasis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, chronic dermal wounds, corneal ulceration, multiple sclerosis, stroke, atherosclerosis, Alzheimer's disease, diabetic retinopathy, macular degeneration, angiofibromas, hemangiomas or angiogenesis. Within this series of heteroaryl succinamides, the following are also included:



Compound	R1	R2	R3	R4	Formula
265776	4-Pyr	H	4-Pyr-NHCO	Me	C ₃₀ H ₃₁ N ₅ O ₄
265777	4-CN-Ph	H	CONHMe	Me	C ₂₈ H ₃₀ N ₄ O ₄
265778	4-Pyr	CH2Ph	CONHMe	Me	C ₃₃ H ₃₆ N ₄ O ₄
265779	CN	H	CONHMe	Me	C ₂₂ H ₂₆ N ₄ O ₄
265780	4-Pyr	H	-COOCH2-		C ₂₅ H ₂₅ N ₃ O ₅
265781	4-Pyr	CH2Ph	-COOCH2-		C ₃₂ H ₃₁ N ₃ O ₅
265782	4-Pyr	H	CH2OH	Me	C ₂₅ H ₂₉ N ₃ O ₄



265783: C21 H26 F N3 O4

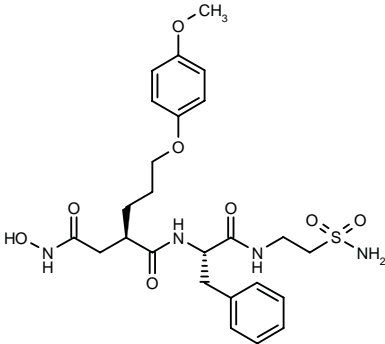
SOURCES – Agouron; Roche Bioscience.

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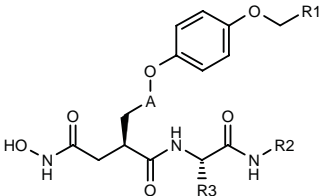
265282

N^α-[2(*R*)-(N-Hydroxycarbamoylmethyl)-5-(4-methoxyphenoxy)pentanoyl]-*N*¹-(2-sulfamoyl-ethyl)-L-phenyl-alaninamide



C25 H34 N4 O8 S; Mol wt: 550.6296

ACTION – A potent inhibitor of matrix metalloproteinases such as gelatinase A (MMP-2; IC₅₀ = 0.36 pM) and gelatinase B (MMP-9; IC₅₀ = 0.051 pM). Other related compounds include the following:



Compound	R1	R2	R3	A	Formula
267093	Me	Me	CH2Ph	-CH2-	C ₂₄ H ₃₁ N ₃ O ₆
267094	H	Me	CH2Ph	-(CH2)2-	C ₂₄ H ₃₁ N ₃ O ₆
267095	H	t-Bu	CH2Ph	-(CH2)2-	C ₂₇ H ₃₇ N ₃ O ₆
267096	Me	Me	CH2Ph	-(CH2)2-	C ₂₅ H ₃₃ N ₃ O ₆
267097	H	Me	CH2Ph	-(CH2)3-	C ₂₅ H ₃₃ N ₃ O ₆
267098	Me	Me	CH2Ph	-(CH2)3-	C ₂₆ H ₃₅ N ₃ O ₆
267099	H	Me	4-MeO-PhCH2	-(CH2)2-	C ₂₅ H ₃₃ N ₃ O ₇
267100	H	CH2CH2-SO2NH2	4-MeO-PhCH2	-(CH2)2-	C ₂₆ H ₃₆ N ₄ O ₉ S
267101	H	Me	4-MeO-PhCH2	-(CH2)3-	C ₂₆ H ₃₅ N ₃ O ₇
267102	H	Me	4-EtO-PhCH2	-(CH2)2-	C ₂₆ H ₃₅ N ₃ O ₇
267103	H	Me	4-EtO-PhCH2	-(CH2)3-	C ₂₇ H ₃₇ N ₃ O ₇
267104	H	Me	t-Bu	-(CH2)2-	C ₂₁ H ₃₃ N ₃ O ₆
267105	H	CH2CH2-SO2NH2	t-Bu	-(CH2)2-	C ₂₂ H ₃₆ N ₄ O ₉ S

SOURCE – Kotobuki.

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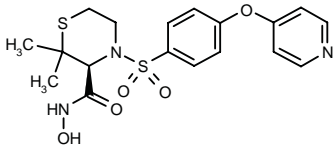
AG-3340

231137
263975* [as (*R*)-enantiomer]

2,2-Dimethyl-4-[4-(4-pyridyloxy)phenylsulfonyl]perhydro-1,4-thiazine-3(*S*)-carbohydroxamic acid

N-Hydroxy-2,2-dimethyl-4-[4-(4-pyridinyloxy)-phenylsulfonyl]thiomorpholine-3(*S*)-carboxamide

AG-3354 (as HCl salt)
AG-3362 (as maleate salt)



C18 H21 N3 O5 S2; Mol wt: 423.5119

ACTION – Synthetic, orally active matrix metalloproteinase (MMP) inhibitor (K_i approx. 30 pM against gelatinase A and B) with potent antiangiogenic activity. Phase II/III clinical trials of AG-3340 in combination with paclitaxel/ carboplatin for the treatment of non-small cell lung cancer and with mitoxantrone/prednisone for the treatment of hormone-refractory prostate cancer have been initiated based on promising antitumor activity (inhibition of primary tumor growth and metastasis) observed in preclinical studies and phase I clinical trials; it also showed a good safety profile in phase I trials.

SOURCE – Agouron.

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22. Agouron and Roche to collaborate on cancer drugs. Agouron Pharmaceuticals, Inc. Press Release 1996, June 20.

23. Agouron initiates pivotal trials of oral anti-angiogenesis drug AG3340 for treatment of lung cancer and prostate cancer. Agouron Pharmaceuticals, Inc. Press Release 1998, May 5.

24. Agouron Pharmaceuticals reports R&D progress. Agouron Pharmaceuticals, Inc. Press Release 1996, Jan 8.

25. Agouron Pharmaceuticals reports recent results from testing of three anti-cancer drugs. Agouron Pharmaceuticals, Inc. Press Release 1996, April 22.

26. Agouron's IND for anticancer agent approved. Daily Essentials 1997, June 20.

27. Agouron's MMP inhibitor AG-3340 enters phase II/III trials. Daily Essentials 1998, May 7.

28. Agouron, Roche terminate cancer collaboration; AG-337 development discontinued. Daily Essentials 1997, Dec 4.

29. Agouron: Annual Report 1997. Daily Essentials 1997, Dec 5.

30. Anticancer MMP inhibitor enters clinical trials. Daily Essentials 1996, Oct 4.

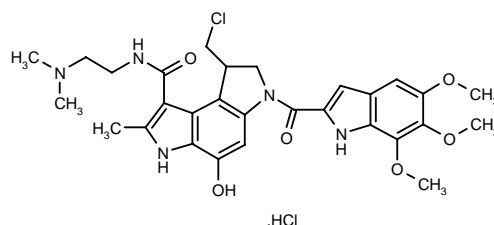
31. Agouron Pharmaceuticals, Inc. Third Quarter Report 1996

*See 263739 Drug Data Report 1998, 020(06): 0542.

MISCELLANEOUS ANTINEOPLASTIC AGENTS

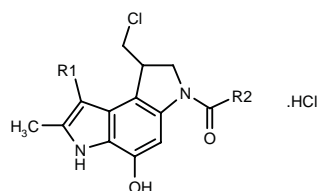
263804

8-(Chloromethyl)-*N*-[2-(dimethylamino)ethyl]-4-hydroxy-2-methyl-6-(5,6,7-trimethoxy-1*H*-indol-2-ylcarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrole-1-carboxamide hydrochloride

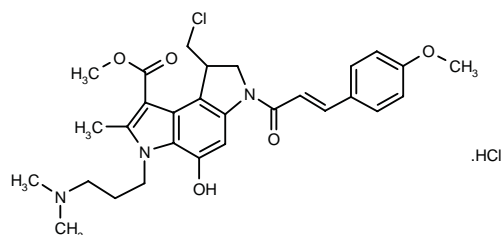


C₂₉ H₃₄ Cl N₅ O₆ . HCl; Mol wt: 620.5305

ACTION – Antineoplastic agent, a water-soluble DC-89 derivative with potent *in vitro* cytotoxicity against human uterine cancer HeLaS3 cells (IC₅₀ = 9.1 nM) and significant antitumor activity *in vivo* in mice bearing s.c. murine sarcoma 180 (T/C = 59% at 0.25 mg/kg i.v.). Other related compounds include the following:



Compound	R1	R2	Formula
267106	CH ₂ N(Me) ₂	5,6,7-(MeO) ₃ -2-indolyl	C ₂₇ H ₃₁ ClN ₄ O ₅ .HCl
267107	4-Me-1-Piz-CO	5,6,7-(MeO) ₃ -2-indolyl	C ₃₀ H ₃₄ ClN ₅ O ₆ .HCl
267108	(S)-CONHCH ₂ CH ₂ S-SCH ₂ CH(NH ₂)CO ₂ Et	5,6,7-(MeO) ₃ -2-indolyl	C ₃₂ H ₃₈ ClN ₅ O ₆ S ₂ .HCl
267109	CH ₂ N(Me) ₂	4-MeO-PhCH=CH	C ₂₈ H ₂₈ ClN ₃ O ₃ .HCl



267110: C₂₉ H₃₄ Cl N₃ O₅.HCl

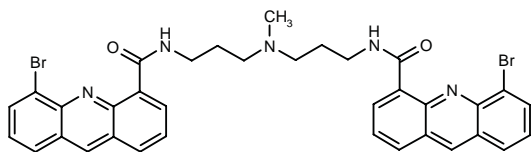
SOURCE – Kyowa Hakko.

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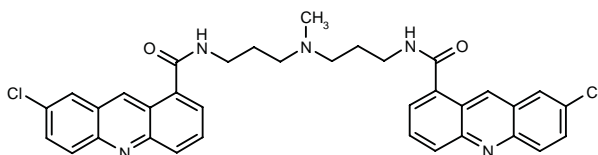
264878

N,N'-(Methylimino)bis(propane-1,3-diyl)bis(5-bromoacridine-4-carboxamide)



C₃₅ H₃₁ Br₂ N₅ O₂; Mol wt: 713.4709

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against murine leukemia P388, murine Lewis lung carcinoma LLTC and wild-type human leukemia Jurkat cells (IC₅₀ = 10, 7 and 28 nM, respectively). *In vivo*, it was shown to inhibit the growth of s.c. colon 38 tumors in mice at 60 mg/kg i.v. Another compound from this series of bisacridine and bisphenazine derivatives is:



266040: C₃₅ H₃₁ Cl₂ N₅ O₂

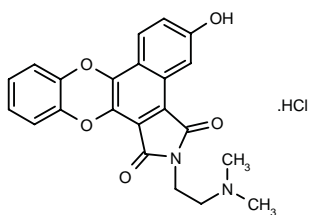
SOURCE – Xenova.

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265157

2-[2-(Dimethylamino)ethyl]-5-hydroxy-2,3-dihydro-1*H*-benzo[*e*][1,4]benzodioxino[2,3-*g*]isoindole-1,3-dione hydrochloride



C₂₂ H₁₈ N₂ O₅ . HCl; Mol wt: 426.8541

ACTION – Antineoplastic agent, a specifically claimed compound from a series of substituted 7,12-dioxabenz[*a*]anthracene derivatives, with good antileukemic activity, as demonstrated *in vitro* against murine leukemia L1210, human epidermoid carcinoma KB-3-1 and human non-small cell lung carcinoma A549 cells, and *in vivo* in mice bearing P388 leukemia.

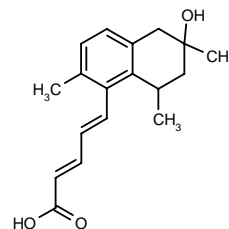
SOURCE – ADIR.

REFERENCES

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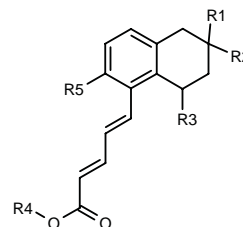
265898

5-(6-Hydroxy-2,6,8-trimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)-2(*E*),4(*E*)-pentadienoic acid

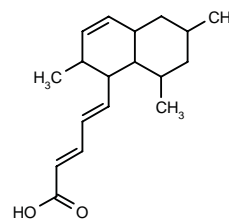


C₁₈ H₂₂ O₃; Mol wt: 286.3688

ACTION – Antioxidant and antineoplastic agent isolated from a culture of *Penicillium citrinum* SCRC-SA124 (FERM P-15765) and also obtainable by chemical synthesis. Antiproliferative activity was shown against murine leukemia P388 cells (IC₅₀ = 29 µg/ml). Compound was also found to inhibit the production of superoxide anion in human leukemia HL-60 cells with an IC₅₀ value of 81 µg/ml. Other compounds from this series of hydronaphthalene derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
266563	H	Me	Me	H	Me	C ₁₈ H ₂₂ O ₂
266565	Me	OH	Me	Me	Me	C ₁₉ H ₂₄ O ₃
266566	H	H	H	H	H	C ₁₈ H ₁₆ O ₂
266567	H	H	H	H	Me	C ₁₈ H ₁₈ O ₂



266564: C₁₈ H₂₆ O₂

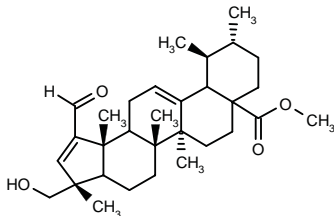
SOURCE – Sagami.

REFERENCES

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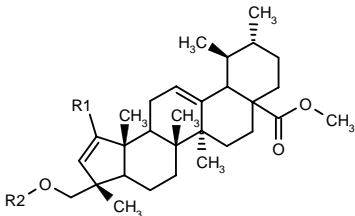
266171

[3*S*-(3 α ,5 α β ,5 β α ,10 α ,11 β ,13 β β)]-1-Formyl-3-(hydroxymethyl)-3,5 α ,5 β ,10,11,13 β -hexamethyl-3 α ,4,5,5 α ,5 β ,6,7,7 α ,8,9,10,11,11 α ,13,13 α ,13 β -hexadecahydro-3*H*-cyclopenta[*a*]chrysene-7 α -carboxylic acid methyl ester

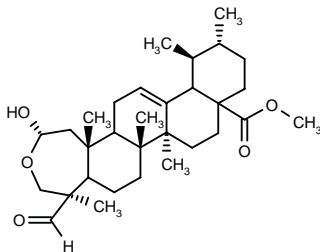


C31 H46 O4; Mol wt: 482.7004

ACTION – Antineoplastic and hepatoprotective agent with *in vitro* cytotoxicity against murine leukemia P388D1 and melanoma Malme-3M (IC₅₀ = 2.4 ± 0.7 and 2.9 ± 0.7 µg/ml, respectively, vs. IC₅₀ = 0.7 ± 0.1 and 1.0 ± 0.2 µg/ml, respectively, for doxorubicin); its activity against P388D1 cells was potentiated when added together with a differentiation promoter. Within this series of asiatic acid derivatives, the following are also included:



Compound	R1	R2	Formula
266865	CHO	COCH2CH2CO2H	C ₃₅ H ₅₀ O ₇
266866	CHO	CO(CH2)3CO2H	C ₃₆ H ₅₂ O ₇
266867	Me	H	C ₃₁ H ₄₈ O ₃



266864: C31 H48 O5

SOURCE – Dong Kook.

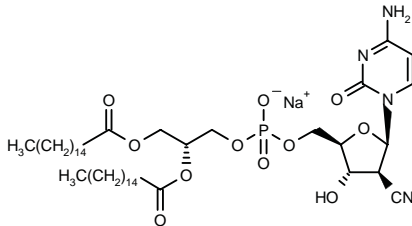
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DPP-CNDAC

266608

(*R*)-4-Amino-1-[5-*O*-[[2,3-bis(hexadecanoyloxy)-propoxy]hydroxyphosphinyl]-2-cyano-2-deoxy- β -D-arabinofuranosyl]-2(1*H*)-pyrimidinone monosodium salt



C45 H78 N4 Na O11 P; Mol wt: 905.0922

ACTION – Antineoplastic nucleoside proven to suppress tumor growth in sarcoma M5076-bearing mice 93 and 98%, respectively, at doses of 100 and 200 mg/kg/day i.p. on days 1, 5 and 9, and increase survival (ILS = 21 and 38%, respectively), although it was toxic at the dose of 300 mg/kg/day i.p. When the nucleoside was incorporated into long-circulating liposomes, it was also effective in suppressing tumor growth and increasing survival in Meth A sarcoma-bearing mice and the liposomal formulations appeared to be associated with reduced toxicity.

SOURCE – Sankyo.

REFERENCES

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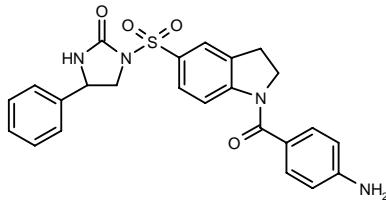
3. Shuto, S. et al. *Nucleosides and nucleotides. 150. Enzymatic synthesis of 5'-phosphatidyl derivatives of 1-(2-C-cyano-2-deoxy- β -D-arabino-pentofuranosyl)-cytosine (CNDAC) and their notable antitumor effects in mice.* Bioorg Med Chem Lett 1996, 6(9): 1021.

DW-2143*

265603

263304 (as hydrochloride)

1-[1-(4-Aminobenzoyl)indolin-5-ylsulfonyl]-4-phenylimidazolidin-2-one



C24 H22 N4 O4 S; Mol wt: 462.5278

ACTION – Orally active sulfonylurea-containing antineoplastic agent with greater cytotoxicity compared to doxorubicin against human lung carcinoma A549 (IC_{50} = 0.20 μ M vs. 1.99 μ M), human chronic myelogenous leukemia K562 (IC_{50} = 0.44 μ M vs. 1.77 μ M) and human ovarian adenocarcinoma SK-OV-3 (IC_{50} = 1.24 μ M vs. 4.15 μ M). Its oral bioavailability in mice was found to be about 40%. DW-2143 was also highly effective in mice bearing murine Lewis lung carcinoma (tumor growth inhibition [TGI] = 84.3% at 100 mg/kg p.o.), murine colon 26 carcinoma (TGI = 55.6% at 65 mg/kg p.o.), human lung carcinoma NCI-H23 (TGI = 67.0% at 65 mg/kg p.o.) and human colon carcinoma SW620 (TGI = 87.0% at 65 mg/kg p.o.) at doses not associated with significant changes in body weight, again being significantly superior to doxorubicin given i.p. at toxicity-limiting doses.

SOURCE – Dong-Wha.

REFERENCES

1. Yoon, S.J. et al. (Dong-Wha Pharmaceuticals Industry Co. Ltd) Arylsulfonyl-imidazolone derivs. as an antitumor agent. WO 9807719.

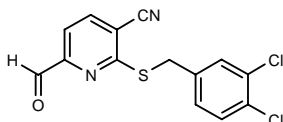
2. Jung, S.-H. et al. Synthesis and antitumor activity of 4-phenyl-1-arylsulfonyl imidazolidinones. Bioorg Med Chem Lett 1998, 8(12): 1547.

*Identified compound **263304** Drug Data Report 1998, 020(06): 0546.

GRN-5384

265235

2-(3,4-Dichlorobenzylsulfanyl)-6-formylpyridine-3-carbonitrile



C14 H8 Cl2 N2 O S; Mol wt: 323.2022

ACTION – Antineoplastic agent that acts by virtue of its ability to inhibit human telomerase activity (IC_{50} = 4.5 μ M). *In vitro* cytotoxicity was evaluated against a panel of ovarian tumor cell lines such as IMR-90, OVCAR-5 and SK-OV-3, giving LD_{50} values of 5, 15 and 10 μ M, respectively. Activity was also demonstrated *in vivo* in mice bearing OVCAR-5 tumors, where compound administered at 25 mg/kg/day p.o. x 50 days was shown to almost completely inhibit tumor growth.

SOURCE – Geron.

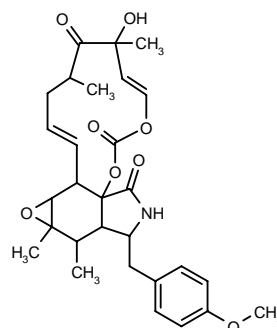
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Mer-WF1726

265270

6-Hydroxy-14-(4-methoxybenzyl)-4,6,15,15a-tetramethyl-3,4,5,6,12,13,14,14a,15,15a,16a,16b-dodecahydro[1,3]dioxacyclotridecino[4,5-d]oxireno[*f*]isoindole-5,10,12-trione



C29 H35 N O8; Mol wt: 525.5945

ACTION – Antineoplastic agent structurally related to cytochalasins, isolated from *Libertella* sp. Mer-WF1726 (FERM P-15680), with *in vitro* cytotoxicity against a range of human tumor cell lines such as leukemia K562, gastric cancer MKN28, lung cancer PC6, breast cancer MCF-7 and colon carcinoma HT29 cells (IC_{50} = 0.68, 13, 60, 12 and 15 μ g/ml, respectively, vs. 8.4, > 100, > 100, > 100 and > 100 μ g/ml, respectively, for cytochalasin E).

SOURCE – Mercian.

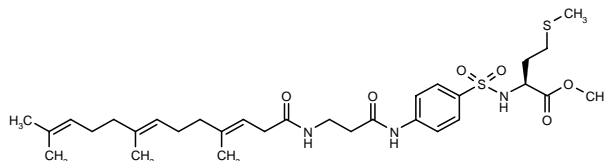
REFERENCES

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SCHL-705

265020

N-[4-[3-[4,8,12-Trimethyl-3(*E*),7(*E*),11-tridecatrienamido]propionamido]phenylsulfonyl]-L-methionine methyl ester



C31 H47 N3 O6 S2; Mol wt: 621.8593

ACTION – Proapoptotic agent, as demonstrated in primary cultures of chick embryo neuronal cells (half-maximal response at 40 μ M), from a series of *N*-substituted *N*^β-homofarnesoyl- β -alanine amides with potential in cancer therapy.

SOURCE – Philipps-Universität Marburg, Marburg (DE).

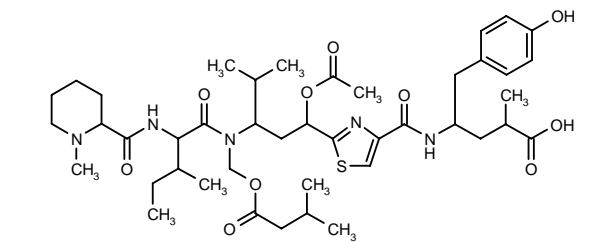
REFERENCES

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TUBULYSIN A

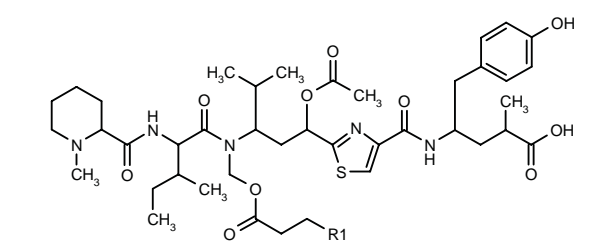
264393

4-[2-[1-Acetoxy-4-methyl-3-[N-(3-methylbutyryl-oxy-methyl)-N-[3-methyl-2-(1-methylpiperidin-2-ylcarboxamido)pentanoyl]amino]pentyl]thiazol-4-ylcarboxamido]-5-(4-hydroxyphenyl)-2-methylpentanoic acid



C43 H65 N5 O10 S; Mol wt: 844.0775

ACTION – Antineoplastic and antifungal agent isolated from the bacteria *Archangium gephyra* DSM 11092, with IC₅₀ values of 0.01, 0.1 and 0.04 ng/ml, respectively, against KB-3-1, K-562 and HL-60 human tumor cell lines. Other compounds from this source are:



Compound	R1	Formula
TUBULYSIN B [267028]	Me	C ₄₂ H ₆₃ N ₅ O ₁₀ S
TUBULYSIN C [267029]	H	C ₄₁ H ₆₁ N ₅ O ₁₀ S

SOURCE – GBF.

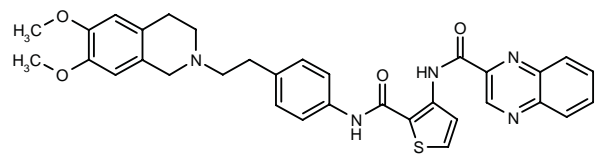
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1. Reichenbach, H. et al. (Gesellschaft für Biotechnologische Forschung mbH) *Cpds. with antimycotic and cytostatic effect, preparation method, agent containing these cpds. and DSM 11 092.* WO 9813375.

RESISTANCE MODIFIERS

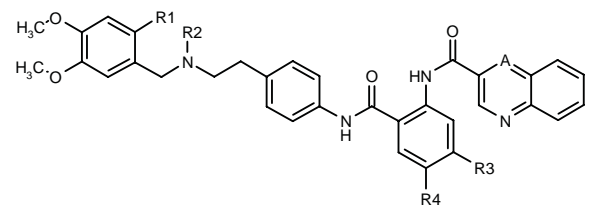
264877

N-[2-[N-[4-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]phenyl]carbamoyl]thiophen-3-yl]quinoxaline-2-carboxamide

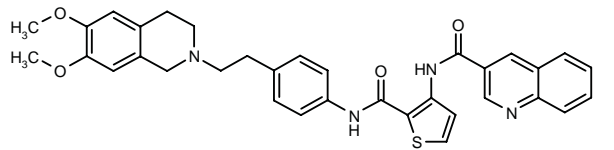


C33 H31 N5 O4 S; Mol wt: 593.7049

ACTION– Multidrug resistance (MDR) modulator that acts by blocking the P-glycoprotein pump system, thus allowing antineoplastic drugs to accumulate in tumor cells. In MDR murine mammary carcinoma AR 1.0 cells, compound was found to increase the accumulation of daunorubicin in the cell and to potentiate the cytotoxicity of doxorubicin; potentiating effects were also observed when compound was administered with paclitaxel in 2780AD cells. Compound is also reported to be useful for improving the absorption, distribution, metabolism and elimination characteristics of a drug. Other specifically claimed compounds from this series of anthranilic acid derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
265876	H	Me	H	H	N	C ₃₄ H ₃₃ N ₅ O ₄
265878	-(CH2)2-		H	N(Me)2	N	C ₃₇ H ₃₈ N ₆ O ₄
265879	-(CH2)2-		OMe	OMe	CH	C ₃₈ H ₃₈ N ₄ O ₆



265877: C34 H32 N4 O4 S

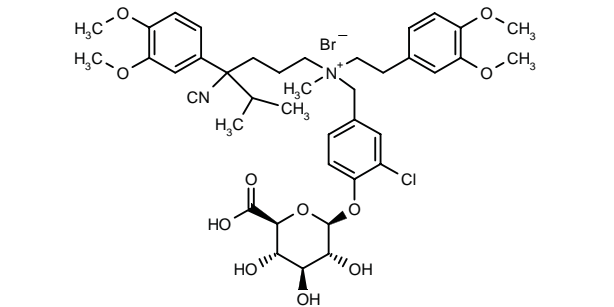
SOURCE – Xenova.

REFERENCES

1. Ryder, H. et al. (Xenova Group plc) *Anthranilic acid derivs. as multi drug resistance modulators.* WO 9817648.

265013

5-[N-[3-Chloro-4-(β-D-glucuronyloxy)benzyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylaminium]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile bromide



C40 H52 Br Cl N2 O11; Mol wt: 852.2108

ACTION – Glucuronic acid prodrug of verapamil for the reversal of multidrug resistance (MDR) that is converted to the latter upon treatment with β -glucuronidase or a fusion protein containing β -glucuronidase. It exhibited marked cytotoxicity in doxorubicin-resistant human colon carcinoma LoVo cells in the presence of the doxorubicin prodrug HMR-1826 and β -glucuronidase or the β -glucuronidase-containing fusion protein.

SOURCE – Hoechst Marion Roussel.

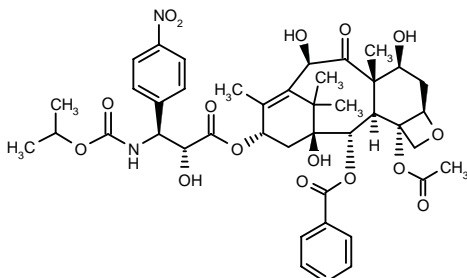
REFERENCES

1. Desbene, S. et al. *Design, synthesis and biological evaluation of a verapamil prodrug for selective MDR reversal at the tumour site*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 559.

RADIATION THERAPY

266093

[2a*R*]-[2 α ,4 β ,4 α β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12 α ,12 $\beta\alpha$]]-12*b*-Acetoxy-12-benzoyloxy-4,6,11-trihydroxy-9-[2-hydroxy-3-(isopropoxycarbonylamino)-3-(4-nitrophenyl)propionyloxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C42 H50 N2 O16; Mol wt: 838.8550

ACTION – Bifunctional paclitaxel derivative that combines potent cytotoxic activity (30-fold more potent against breast adenocarcinoma MCF-7 cells than paclitaxel) with radiosensitizing properties, a strategy expected to offer significant advantages in the therapy of cancer.

SOURCE – VivoRx.

REFERENCES

1. Tao, C. et al. *Nitrophenyl, 10-deacetylated subst. Taxol derivs. as dual functional cytotoxic/radiosensitizers*. US 5780653.

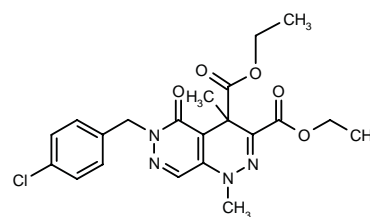
OCULAR MEDICATIONS

ANTI GLAUCOMA AGENTS

CK-119

266605

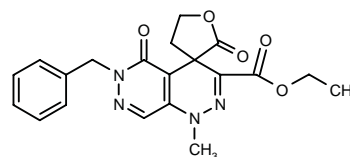
6-(4-Chlorobenzyl)-1,4-dimethyl-5-oxo-1,4,5,6-tetrahydropyridazino[4,5-*c*]pyridazine-3,4-dicarboxylic acid diethyl ester



C21 H23 Cl N4 O5; Mol wt: 446.8887

M.p 149-50 °C.

ACTION – Potent IL-1 blocker proven to inhibit the growth of corneal fibroblasts (30-300 mg/l) and conjunctival cells (3-30 mg/l) mainly via inhibition of DNA and RNA synthesis. It also inhibited posterior uveitis induced by intravitreal IL-1. Potentially useful for improving the success rate of filtration surgery in the treatment of glaucoma. Another dihydropyridazino-pyridazine derivative with a similar profile is:



CK-122 [266606]: C20 H20 N4 O5

SOURCE – Texas A&M University, College Station, TX (US).

REFERENCES

1. Xuan, B. and Chiou, C.Y. *Inhibition of fibroblast-like cell proliferation by interleukin-1 blockers, CK-119 and CK-122*. Acta Pharmacol Sin 1998, 19(4): 304.

ACTION – Glucuronic acid prodrug of verapamil for the reversal of multidrug resistance (MDR) that is converted to the latter upon treatment with β -glucuronidase or a fusion protein containing β -glucuronidase. It exhibited marked cytotoxicity in doxorubicin-resistant human colon carcinoma LoVo cells in the presence of the doxorubicin prodrug HMR-1826 and β -glucuronidase or the β -glucuronidase-containing fusion protein.

SOURCE – Hoechst Marion Roussel.

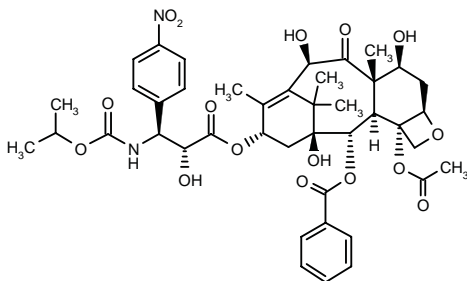
REFERENCES

1. Desbene, S. et al. *Design, synthesis and biological evaluation of a verapamil prodrug for selective MDR reversal at the tumour site*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 559.

RADIATION THERAPY

266093

[2a*R*]-[2 α ,4 β ,4 α β ,6 β ,9 α (2*R*,3*S*),11 β ,12 α ,12 α ,12 β]-12*b*-Acetoxy-12-benzoyloxy-4,6,11-trihydroxy-9-[2-hydroxy-3-(isopropoxycarbonylamino)-3-(4-nitrophenyl)propionyloxy-4*a*,8,13,13-tetramethyl-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benz[1,2-*b*]oxet-5-one



C42 H50 N2 O16; Mol wt: 838.8550

ACTION – Bifunctional paclitaxel derivative that combines potent cytotoxic activity (30-fold more potent against breast adenocarcinoma MCF-7 cells than paclitaxel) with radiosensitizing properties, a strategy expected to offer significant advantages in the therapy of cancer.

SOURCE – VivoRx.

REFERENCES

1. Tao, C. et al. *Nitrophenyl, 10-deacetylated subst. Taxol derivs. as dual functional cytotoxic/radiosensitizers*. US 5780653.

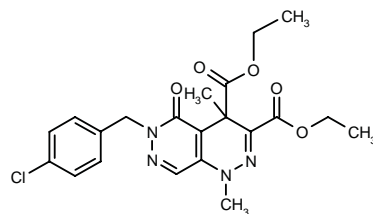
OCULAR MEDICATIONS

ANTI GLAUCOMA AGENTS

CK-119

266605

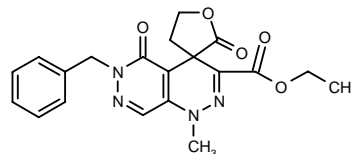
6-(4-Chlorobenzyl)-1,4-dimethyl-5-oxo-1,4,5,6-tetrahydropyridazino[4,5-*c*]pyridazine-3,4-dicarboxylic acid diethyl ester



C21 H23 Cl N4 O5; Mol wt: 446.8887

M.p 149-50 °C.

ACTION – Potent IL-1 blocker proven to inhibit the growth of corneal fibroblasts (30-300 mg/l) and conjunctival cells (3-30 mg/l) mainly via inhibition of DNA and RNA synthesis. It also inhibited posterior uveitis induced by intravitreal IL-1. Potentially useful for improving the success rate of filtration surgery in the treatment of glaucoma. Another dihydropyridazino-pyridazine derivative with a similar profile is:



CK-122 [266606]: C20 H20 N4 O5

SOURCE – Texas A&M University, College Station, TX (US).

REFERENCES

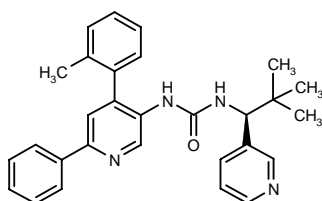
1. Xuan, B. and Chiou, C.Y. *Inhibition of fibroblast-like cell proliferation by interleukin-1 blockers, CK-119 and CK-122*. Acta Pharmacol Sin 1998, 19(4): 304.

METABOLIC DRUGS

TREATMENT OF LIPOPROTEIN DISORDERS

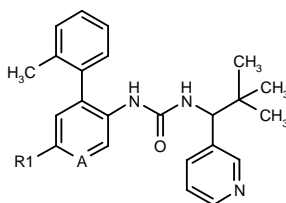
265483

N-[2,2-Dimethyl-1 (*S*)-(3-pyridyl)propyl]-*N'*-[4-(2-methylphenyl)-6-phenylpyridin-3-yl]urea



C29 H30 N4 O; Mol wt: 450.5830

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of ACAT (IC₅₀ = 54.2 ng/ml using enzyme from rat hepatic microsomes). Other compounds from this series of arylureas or arylmethylcarbamoyl derivatives include the following:



Compound	R1	A	Formula
265966	OBu	CH	C ₂₈ H ₃₅ N ₃ O ₂
265967	OCH ₂ Ph	CH	C ₃₁ H ₃₃ N ₃ O ₂
265968	Ph	N	C ₂₉ H ₃₀ N ₄ O

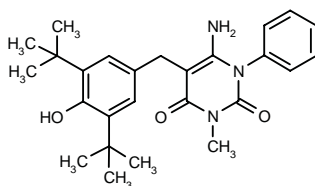
SOURCE – Sankyo.

REFERENCES

1. Yanagisawa, H. et al. (Sankyo Co., Ltd.) *Arylureas or arylmethylcarbamoyl derivs.* WO 9821185, JP 98182608.

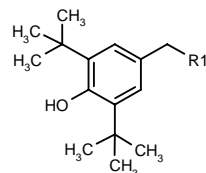
265272

6-Amino-5-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-3-methyl-1-phenyluracil



C26 H33 N3 O3; Mol wt: 435.5647

ACTION – Hypolipidemic agent proven to reduce plasma cholesterol levels in rats fed a diet supplemented with 1% cholesterol (58.0% decrease at 10 mg/kg/day p.o. x 7 days). Other compounds from this series of phenol derivatives include the following:



Compound	R1	Formula
265945	1-Me-3-Ph-2,4,6-trioxo-hexahydro-5-pyrimidinyl	C ₂₆ H ₃₂ N ₂ O ₄
265946	6-NH ₂ -3-Me-1-Ph-uracil-5-yl-NH	C ₂₆ H ₃₄ N ₄ O ₃

SOURCE – Japan Energy.

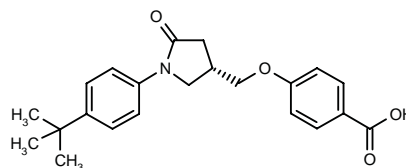
REFERENCES

1. Isobe, Y. and Matsui, J. (Japan Energy Corp.) *Novel phenol derivs. and their use as medicine.* JP 98114754.

265973

169937 (as racemic)*

(*S*)-(+)-4-[1-(4-*tert*-Butylphenyl)-2-oxo-4-pyrrolidinyl-methoxy]benzoic acid



C22 H25 N O4; Mol wt: 367.4425

ACTION – Dual hypolipidemic and hypocholesterolemic agent with potent inhibitory effects on the biosynthesis of both fatty acids and sterols. In WHHL rabbits, it was more potent than pravastatin in reducing total cholesterol levels (ED₁₅ = 1.3 mg/kg/day p.o. vs. 19.5 mg/kg/day p.o.) and, unlike pravastatin, it also significantly reduced serum triglycerides (ED₃₀ = 4.2 mg/kg/day p.o.). It appears to act by inhibiting VLDL particle formation.

SOURCE – Taiho.

REFERENCES

1. Fujii, S. et al. (Otsuka Pharmaceutical Co., Ltd.) *Phenylcarboxylic acid derivs. having hetero ring.* EP 393607, JP 91275666, US 5145865.

2. Ogawa, K. et al. (Taiho Pharmaceutical Co., Ltd.) *Preparation method of optically active 1-(4-tert-butylphenyl)-5-oxo-3-pyrrolidine carboxylate.* JP 98192221.

3. Yano, S. et al. (Taiho Pharmaceutical Co., Ltd.) *Optically active 1-phenylpyrrolidine derivative, intermediate for producing the same, and process for producing both.* WO 9406767.

4. Ogawa, K. et al. *Synthesis of 4-[1-(substituted phenyl)-2-oxo-pyrrolidin-4-yl]-methoxybenzoic acids and related compounds, and their fatty acids and sterols biosynthesis inhibitory capacities.* 13th Int Symp Med Chem (Sept 19-23, Paris) 1994, Abst P85.

5. Ohmori, K. et al. *New benzoic acid derivative (S-2E) reduces both cholesterol and triglyceride levels as a VLDL particle formation inhibitor.* 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 52.

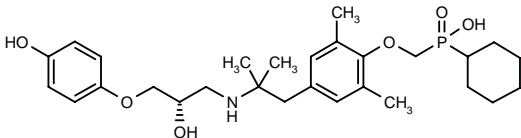
6. Watanabe, S. et al. *Synthesis of 4-[1-(substituted phenyl)-2-oxo-pyrrolidin-4-yl]methoxybenzoic acids and related compounds, and their inhibitory capacities toward fatty-acid and sterol biosyntheses.* Eur J Med Chem 1994, 29(9): 675.

*See **167121** Drug Data Report 1991, 013(04): 0325.

ANTIOBESITY DRUGS

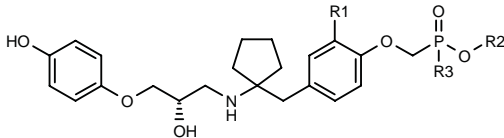
265525

Cyclohexyl[4-[2-[2(S)-hydroxy-3-(4-hydroxyphenoxy)-propylamino]-2-methylpropyl]-2,6-dimethylphenoxy-methyl]phosphinic acid



C28 H42 N O6 P; Mol wt: 519.6148

ACTION – Agent for the treatment of obesity and diabetes, a β_3 -adrenoceptor agonist with antagonist activity at β_1 - and β_2 -adrenoceptors. Also claimed for the treatment of gastrointestinal disorders, esophagitis, gastritis, duodenitis, intestinal ulcerations, irritable bowel syndrome, gastrointestinal ulcerations and depression. Other specifically claimed compounds from this series of phosphorus-containing propanolamine derivatives include the following:



Compound	R1	R2	R3	Formula
266522	H	H	Ph	C ₂₈ H ₃₄ NO ₆ P
266523	Br	H	cyclohexyl	C ₂₈ H ₃₉ BrNO ₆ P
266524	Br	cyclohexyl	cyclohexyl-O	C ₃₄ H ₄₉ BrNO ₇ P
266525	H	H	cyclohexyl	C ₂₈ H ₄₀ NO ₆ P

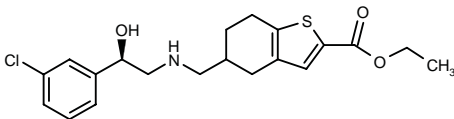
SOURCE – SmithKline Beecham.

REFERENCES

1. Beeley, L.J. et al. (SmithKline Beecham plc) *Phosphorus containing aryloxy or arylthiopropylamine derivs.* WO 9822480.

265909

5-[2(R)-(3-Chlorophenyl)-2-hydroxyethylaminomethyl]-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylic acid ethyl ester



C20 H24 Cl N O3 S; Mol wt: 393.9326

ACTION – Potent and selective β_3 -adrenoceptor agonist (EC_{50} = 8.8 nM in rat colon preparations) with negligible activity at β_1 - and β_2 -adrenoceptors (EC_{50} = 30,000 nM or more). A representative compound from a series of tetrahydrobenzo[b]thiophene derivatives.

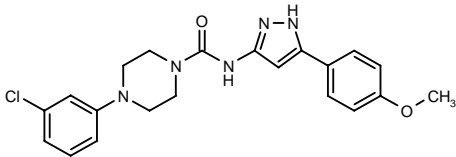
SOURCE – Tokyo Tanabe.

REFERENCES

1. Tsuchiya, T. and Matsumoto, H. (Tokyo Tanabe Co., Ltd.) *Tetrahydrobenzothiophene derivs.* JP 98152488.

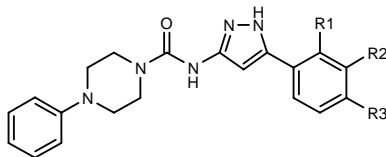
266215

4-(3-Chlorophenyl)-N-[5-(4-methoxyphenyl)pyrazol-3-yl]piperazine-1-carboxamide



C21 H22 Cl N5 O2; Mol wt: 411.8908

ACTION – Agent for the treatment of obesity, hyperphagia and diabetes that acts by virtue of its neuropeptide Y (NPY) Y_5 receptor-antagonist activity (IC_{50} = 27 nM). It is reported to significantly inhibit the increase in food intake induced by bPP in rats. A representative compound from a series of urea derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
267191	H	H	OMe	C ₂₁ H ₂₃ N ₅ O ₂
267192	H	H	Cl	C ₂₀ H ₂₀ ClN ₅ O
267193	Me	H	H	C ₂₁ H ₂₃ N ₅ O
267194	H	Me	H	C ₂₁ H ₂₃ N ₅ O

SOURCE – Banyu.

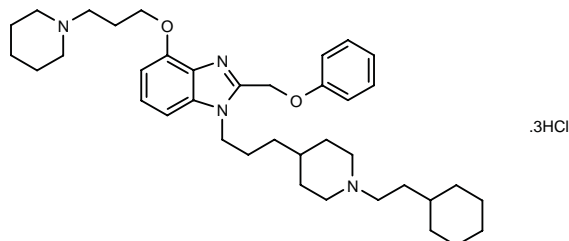
REFERENCES

1. Fukami, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel urea derivs.* WO 9824768.

LY-366337

265293

1-[3-[1-(2-Cyclohexylethyl)-4-piperidinyl]propyl]-2-(phenoxymethyl)-4-[3-(1-piperidinyl)propoxy]benzimidazole trihydrochloride



C₃₈ H₅₆ N₄ O₂ · 3 HCl; Mol wt: 710.2691

ACTION – Highly potent and selective neuropeptide Y (NPY) Y₁ receptor antagonist, as determined in binding studies using human Y₁ (K_i = 0.29 nM), Y₂, Y₄ and Y₅ receptors (K_i > 1000 nM for all three subtypes), and *ex vivo* in rat brain by inhibition of [¹²⁵I]-LP-PYY binding (ED₅₀ = 9.8 mg/kg s.c.). The compound reduced food consumption, body weight, blood glucose and plasma corticosterone levels in *ob/ob* mice at a dose of 30 mg/kg/day s.c. for 7 days. Potentially useful in the treatment of obesity.

SOURCE – Lilly.

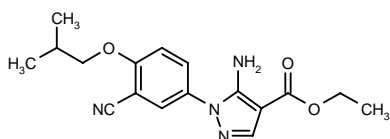
REFERENCES

1. Gehlert, D.R. *Neuropeptide Y antagonists: Potential for the treatment of obesity*. IBC 5th Int Symp Ther Adv Obes (March 30-31, McLean) 1998.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

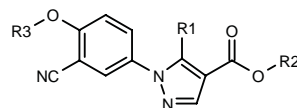
265104

5-Amino-1-(3-cyano-4-isobutoxyphenyl)pyrazole-4-carboxylic acid ethyl ester



C₁₇ H₂₀ N₄ O₃; Mol wt: 328.3700

ACTION – Xanthine oxidase inhibitor with potential in the treatment of hyperuricemia and gout. A representative compound from a series of 1-phenylpyrazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
266275	NH ₂	H	i-Bu	C ₁₅ H ₁₆ N ₄ O ₃
266276	H	Et	i-Bu	C ₁₇ H ₁₉ N ₃ O ₃
266277	H	H	i-Bu	C ₁₅ H ₁₅ N ₃ O ₃
266278	H	Et	C ₆ H ₁₃	C ₁₉ H ₂₃ N ₃ O ₃
266279	H	H	C ₆ H ₁₃	C ₁₇ H ₁₉ N ₃ O ₃
266280	H	Et	cyclopentyl	C ₁₈ H ₁₉ N ₃ O ₃
266281	H	H	cyclopentyl	C ₁₆ H ₁₅ N ₃ O ₃
266282	H	Et	cyclohexyl	C ₁₉ H ₂₁ N ₃ O ₃
266283	H	H	cyclohexyl	C ₁₇ H ₁₇ N ₃ O ₃

SOURCE – Yoshitomi.

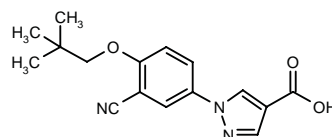
REFERENCES

1. Ishibuchi, S. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *1-Phenylpyrazole cpds. and medicinal application thereof*. WO 9818765.

Y-700

266318

1-[3-Cyano-4-(2,2-dimethylpropoxy)]-1H-pyrazole-4-carboxylic acid



C₁₆ H₁₇ N₃ O₃; Mol wt: 299.3283

White crystalline powder, m.p. 198 °C.

ACTION – Xanthine oxidase inhibitor proven effective in inhibiting enzyme from bovine milk, rat and cynomolgus monkey liver (IC₅₀ = 4.3-6.5 nM), being 50 times more potent than allopurinol (IC₅₀ = 250-360 nM). Y-700 showed potent and long-lasting hypouricemic activity in oxonate-treated rats following oral administration (ED₃₀ = 1.3 and 3.4 mg/kg, respectively, at 2 and 10 h after drug administration; allopurinol: ED₃₀ = 3.3 and > 10 mg/kg, respectively). In inosine-treated rats, both Y-700 and allopurinol decreased uric acid levels in plasma (ED₃₀ = 2.5 and 6.7 mg/kg, respectively, at 2 h). Title compound was found to be 20 times more potent than allopurinol in increasing urinary oxypurine levels after subchronic oral treatment (0.1-3.0 mg/kg x 2 weeks); no tolerance was detected with either compound. Potentially useful for the treatment of hyperuricemia and gout.

SOURCE – Yoshitomi.

REFERENCES

1. Ishibuchi, S. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *1-Phenylpyrazole cpds. and medicinal application thereof*. WO 9818765.

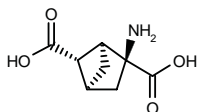
2. Fukunari, A. et al. *Hypouricemic activity of Y-700, a new class of xanthine oxidase inhibitor*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.32.

PHARMACOLOGICAL TOOLS

ABHxD-I

264590

(1*S*,2*S*,4*S*,5*S*)-2-Aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid



C₈ H₁₁ N O₄; Mol wt: 185.1779

Hydrochloride, *m.p.* > 220 °C, $[\alpha]_D^{25} +15^\circ$ (*c* 0.5, MeOH).

ACTION – Conformationally restricted ACPD analog shown to be more potent than the latter at all eight metabotropic glutamate receptor (mGluR) subtypes and comparable in potency to the endogenous ligand glutamate; it gave EC₅₀ values for the group I receptors mGluR1a and mGluR5a of 1.6 and 0.72 μM, respectively, for the group II receptors mGluR2 and mGluR3/1a of 0.33 and 2.2 μM, respectively, and for the group III receptors mGluR4a and mGluR6 of 23 and 5.3 μM, respectively. It thus shows, similar to glutamate, little subtype selectivity. Activity at ionotropic glutamate receptors was observed only at much higher concentrations. It is suggested to be a good lead compound for the design of subtype-selective mGluR ligands.

SOURCE – Georgetown University Med. Center, Washington, DC (US).

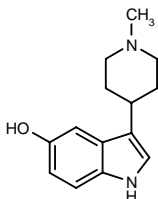
REFERENCES

1. Kozikowski, A.P. et al. *Synthesis and biology of the conformationally restricted ACPD analogue, 2-aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid-I, a potent mGluR agonist.* J Med Chem 1998, 41(10): 1641.

BRL-54443

264070

3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-ol



C₁₄ H₁₈ N₂ O; Mol wt: 230.3092

ACTION – Potent and selective agonist at 5-ht_{1E} and 5-ht_{1F} receptors ($pK_i = 8.7 \pm 0.1$ and 8.9 ± 0.1 , respectively) with at least 30-fold selectivity over other 5-HT receptors and dopamine receptors and α_{1B} -adrenoceptors ($pK_i = 5.9$ -7.2). The compound demonstrated full agonist activity at 5-ht_{1E} ($pEC_{50} = 8.5 \pm 0.1$) and 5-ht_{1F} receptors ($pEC_{50} = 8.6 \pm 0.1$), and it also acted as a full agonist at 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors. Potentially useful as a tool for elucidating the physiological role of the 5-ht_{1E} and 5-ht_{1F} receptors.

SOURCE – SmithKline Beecham.

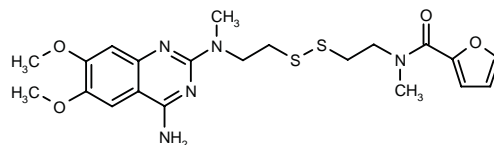
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1. Brown, A.M. et al. *BRL 54443, a potent agonist with selectivity for human cloned 5-ht_{1E} and 5-ht_{1F} receptors.* Br J Pharmacol 1998, 123(Suppl.): Abst 233P.
2. Lightowler, S. et al. *Effect of BRL 54443 (3-(1-methylpiperidin-4-yl)-1H-indol-5-ol), a 5-HT_{1E/1F} receptor agonist, on general behaviour and maximal electroshock seizure threshold in the rat.* Br J Pharmacol 1998, 123(Suppl.): Abst 237P.

CYSTAZOSIN

264964

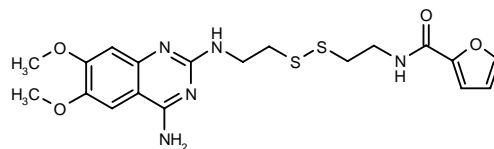
N-[2-[2-[*N*-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-*N*-methylamino]ethyl]disulfanyl]ethyl]-*N*-methylfurane-2-carboxamide



C₂₁ H₂₇ N₅ O₄ S₂; Mol wt: 477.6073

M.p. 180-4 °C.

ACTION – Functionally selective α_{1D} -adrenoceptor antagonist ($pA_2 = 8.54$ in rat thoracic aorta; $pA_2 = 7.53$ in rat prostatic vas deferens [α_{1A}]; $pA_2 = 7.49$ in rat spleen [α_{1B}]), with little or no affinity for α_2 -adrenoceptors (rat cortex; $pK_i = 6.23$), dopamine D₂ (rat striatum; $pK_i = 5$ or less) or 5-HT_{1A} receptors (cloned human; $pK_i < 6$). It is suggested to represent a valuable tool for the pharmacological identification of α_1 -adrenoceptor subtypes in functional assays. However, in binding studies using cloned human α_1 -adrenoceptor subtypes, it did not show the same selectivity observed in functional assays, exhibiting a substantial increase in affinity for the α_{1A} - and α_{1B} -adrenoceptor subtypes. Another prazosin-related quinazoline is:



265562: C₁₉ H₂₃ N₅ O₄ S₂

SOURCE – Recordati.

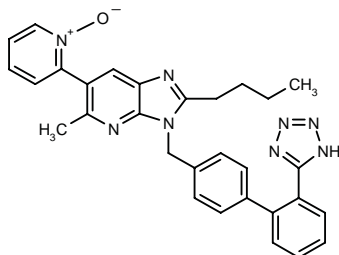
REFERENCES

1. Minarini, A. et al. *Search for α_1 -adrenoceptor subtypes selective antagonists: Design, synthesis and biological activity of cystazosin, an α_{1D} -adrenoceptor antagonist.* Bioorg Med Chem Lett 1998, 8(11): 1353.

KR-31080

262697

2-Butyl-5-methyl-6-(1-oxido-2-pyridinyl)-3-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-3*H*-imidazo[4,5-*b*]pyridine



C30 H28 N8 O; Mol wt: 516.6062

ACTION – Potent, selective and competitive, nonpeptide angiotensin II (All) AT₁ receptor antagonist belonging to a new class; it inhibited [¹²⁵I]-All binding to rabbit aortic membranes and [¹²⁵I]-[Sar¹,Ile⁸]-All binding to human recominant AT₁ receptors with IC₅₀ values of 0.84 ± 0.08 and 1.92 ± 0.15 nM, respectively, whereas it had no effect against AT₂ receptors ([¹²⁵I]-All binding to bovine cerebellum membranes). The compound produced insurmountable antagonism of All-induced contractions of isolated rabbit aortic segments (pD'₂ = 10.1 ± 0.1), without affecting norepinephrine-induced contractions. Potentially useful as a tool for investigating the physiological and pharmacological actions of All, as well as for the development of antihypertensive and antiproliferative drugs.

SOURCE – Korea Res. Inst. Chem. Technol., Daejeon (KR).

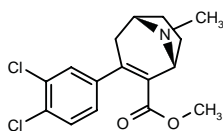
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2. Hong, K.W. et al. *The in vitro pharmacological profile of KR31080, a nonpeptide AT₁ receptor antagonist*. Fundam Clin Pharmacol 1998, 12(1): 64.
3. Lee, W. et al. *Effect of brain angiotensin II AT₁, AT₂, and cholinergic receptor antagonism on drinking in water-deprived rats*. Regul Pept 1996, 66(1-2): 41.

O-1109²

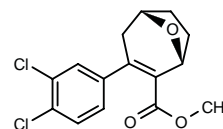
266344

(1*R*,5*S*)-3-(3,4-Dichlorophenyl)-8-methyl-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid methyl ester



C16 H17 Cl₂ N O₂; Mol wt: 326.2213

ACTION – Potent monoamine transport inhibitor shown to bind to the dopamine transporter with high affinity (IC₅₀ = 1.6 ± 0.15 nM) and > 700-fold selectivity relative to the serotonin transporter. Compound crossed the blood–brain barrier to produce effects comparable to those observed with other monoamine transport inhibitors. Another nonamine compound with a similar pharmacological profile is:



O-1059 [266345]¹⁻³: C₁₅ H₁₄ Cl₂ O₃

SOURCE – Organix.

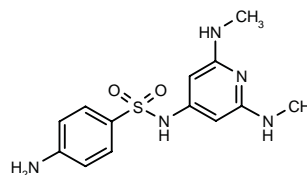
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1. Madras, B.K. and Meltzer, P. (Organix, Inc.; Harvard College) *Bridge-subst. tropanes for methods of imaging and therapy*. US 5770180.
2. Madras, B.K. et al. *Monoamine transporters: Novel insights with novel nonamines*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.181.
3. Meltzer, P.C. et al. *2-Carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes: Potent non-nitrogen inhibitors of monoamine transporters*. J Med Chem 1998, 40(17): 2661.

RO-63-0563¹⁻³

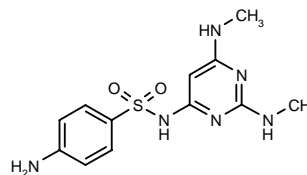
265030

4-Amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]-benzenesulfonamide



C₁₃ H₁₇ N₅ O₂ S; Mol wt: 307.3763

ACTION – Potent and selective 5-HT₆ (now known as 5-HT_{1F}) receptor antagonist shown in binding studies using [³H]-LSD as the ligand and rat and human receptors to have pK_i values of 7.83 ± 0.01 and 7.91 ± 0.02, respectively; it was 100-fold selective for the 5-HT₆ receptor relative to a number of other receptors and binding sites. The compound demonstrated no agonist or inverse agonist effects in functional studies measuring cAMP accumulation in HeLa cells stably expressing the human 5-HT₆ receptor, but acted as a competitive antagonist (pA₂ = 7.10 ± 0.09). Potentially useful as a pharmacological tool for the identification of 5-HT₆ receptors and elucidation of their physiological function. Another related compound with a similar profile is:



Ro-04-6790 [265031]^{1,3}: C₁₂ H₁₆ N₆ O₂ S

SOURCE – Roche.

REFERENCES

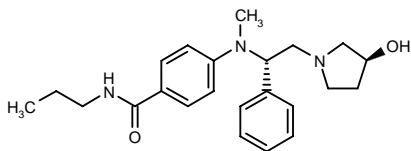
1. Börs, M. et al. (F. Hoffmann-La Roche AG) *Sulphonamides and their use*. EP 815861, JP 98067734.
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3. Sleight, A.J. et al. *Characterization of Ro 04-6790 and Ro 63-0563: Potent and selective antagonists at human and rat 5-HT₆ receptors*. Br J Pharmacol 1998, 124(3): 556.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

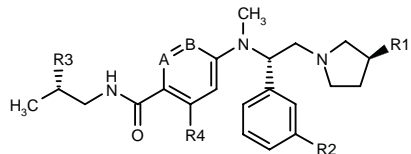
263884

4-[N-[2-[3(S)-Hydroxypyrrolidin-1-yl]-1(S)-phenylethyl]-N-methylamino]-N-propylbenzamide

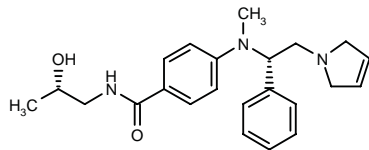


C23 H31 N3 O2; Mol wt: 381.5169

ACTION – Selective κ -opioid receptor agonist claimed for use as an analgesic, anesthetic, antiinflammatory and neuroprotective agent, as well as for the treatment of arthritis, stroke or functional bowel disease. Within this series of pyrrolidiny and pyrrolinyl ethylamine compounds, the following are also specifically claimed:



Compound	R1	R2	R3	R4	A	B	Formula
266431	OH	H	H	OMe	CH	CH	C ₂₄ H ₃₃ N ₃ O ₃
266432	OH	H	H	H	CH	N	C ₂₂ H ₃₀ N ₄ O ₂
266433	OH	OCH ₂ CO ₂ H	H	H	CH	CH	C ₂₅ H ₃₃ N ₃ O ₅
266434	F	H	H	H	CH	CH	C ₂₃ H ₃₀ FN ₃ O
266435	OH	H	OH	H	CH	CH	C ₂₃ H ₃₁ N ₃ O ₃
266436	F	H	OH	H	N	CH	C ₂₂ H ₂₉ FN ₄ O ₂
266438	Cl	H	OH	H	CH	CH	C ₂₃ H ₃₀ ClN ₃ O ₂



266437: C23 H29 N3 O2

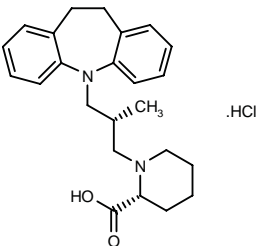
SOURCE – Pfizer.

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1. Ito, F. and Kondo, H. (Pfizer Inc.) *Pyrrolidiny and pyrrolinyl ethylamine cpds. as kappa agonists*. WO 9812177.

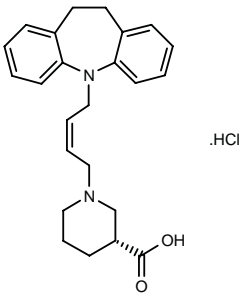
264433

1-[3-(10,11-Dihydro-5H-dibenzo[*b,f*]azepin-5-yl)-2(*R*)-methylpropyl]piperidine-2(*R*)-carboxylic acid hydrochloride



C24 H30 N2 O2 . HCl; Mol wt: 414.9739

ACTION – Analgesic and antiinflammatory agent that inhibits neurogenic inflammation involving the release of neuropeptides from peripheral and central endings of sensory C-fibers. Compound gave 47% inhibition of histamine-induced paw edema in rats at 1.0 mg/kg i.p. Also useful for the treatment of insulin resistance in non-insulin-dependent diabetes mellitus by virtue of its ability to inhibit the secretion and circulation of insulin-antagonizing peptides such as CGRP and amylin. Another compound from this series of *N*-substituted azaheterocyclic derivatives is:



267687: C24 H28 N2 O2 . HCl

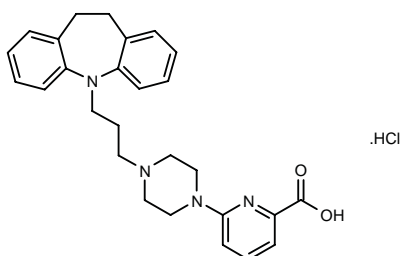
SOURCE – Novo Nordisk.

REFERENCES

1. Jorgensen, T.K. et al. (Novo Nordisk A/S) *N-Substd. azaheterocyclic cpds*. WO 9815546.

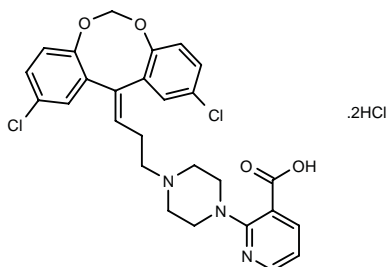
264435

6-[4-[3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)propyl]-piperazin-1-yl]pyridine-2-carboxylic acid hydrochloride



C27 H30 N4 O2 . HCl; Mol wt: 479.0209

ACTION – Analgesic and antiinflammatory agent for the treatment of painful, hyperalgesic and/or inflammatory conditions in which C-fibers play a role. Compound gave 61% inhibition of histamine-induced paw edema in rats at 1.0 mg/kg i.p. Also reported to be useful for the treatment of insulin resistance in non-insulin-dependent diabetes mellitus by virtue of its ability to inhibit the secretion and circulation of insulin-antagonizing peptides such as CGRP and amylin. Another compound from this series of 1,4-disubstituted piperazines is:



267696: C27 H25 Cl2 N3 O4 . 2HCl

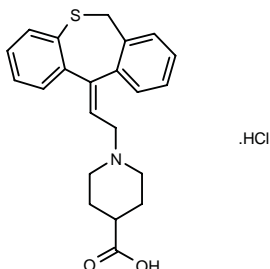
SOURCE – Novo Nordisk.

REFERENCES

1. Hohlweg, R. et al. (Novo Nordisk A/S) 1,4-Disubst. piperazines. WO 9815548.

264436

1-[2-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-ylidene)ethyl]-piperidine-4-carboxylic acid hydrochloride



C22 H23 N O2 S . HCl; Mol wt: 401.9556

ACTION – Analgesic and antiinflammatory agent that acts by inhibiting neurogenic inflammation involving the release of neuropeptides from peripheral and central endings of sensory C-fibers. Compound gave 51% inhibition of histamine-induced paw edema in rats at 1 mg/kg i.p. Also reported to be useful for the treatment of

insulin resistance in non-insulin-dependent diabetes mellitus by virtue of its ability to inhibit the secretion and circulation of insulin-antagonizing peptides such as CGRP and amylin.

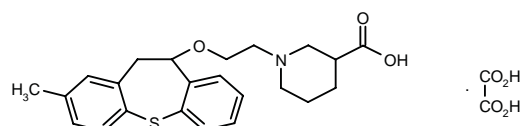
SOURCE – Novo Nordisk.

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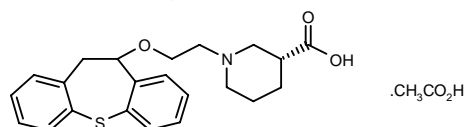
264437

1-[2-(2-Methyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-yloxy)ethyl]piperidine-3-carboxylic acid hydrogen oxalate



C23 H27 N O3 S . C2 H2 O4; Mol wt: 487.5701

ACTION – Analgesic and antiinflammatory agent that acts by inhibiting neurogenic inflammation caused by the release of neuropeptides from peripheral and central endings of sensory C-fibers. Compound gave 49% inhibition of histamine-induced paw edema in rats at 1 mg/kg i.p. Also reported to be useful for the treatment of insulin resistance in non-insulin-dependent diabetes mellitus by virtue of its ability to inhibit the secretion and circulation of insulin-antagonizing peptides such as CGRP and amylin. Another compound from this series of *N*-substituted azaheterocyclic derivatives is:



267693: C22 H25 N O3 S . C2 H4 O2

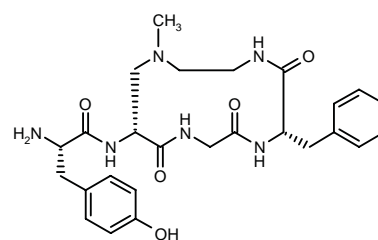
SOURCE – Novo Nordisk.

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266058

L-Tyrosine *N*-[6(*S*)-benzyl-1-methyl-5,8,11-trioxo-1,2,7,10-tetraazacyclotridecan-12(*R*)-yl]amide



C26 H34 N6 O5; Mol wt: 510.5916

ACTION – Potent and broad-spectrum opioid agonist, an enkephalin analog with high affinity for μ - and δ -opioid receptors ($K_i = 1.6$ and 2.1 nM, respectively) and moderate affinity for the κ -opioid receptor ($K_i = 340$ nM). In the *in vivo* thermal escape assay in rats, it had an ED_{50} of 0.027 μ g intrathecally, an effect that was reversed by naloxone, compared to values of 0.14 , 2.4 and 54 μ g, respectively, for DAMGO, morphine and DPDPE. Potential new lead compound in the search for high-efficacy and selective enkephalin analogs.

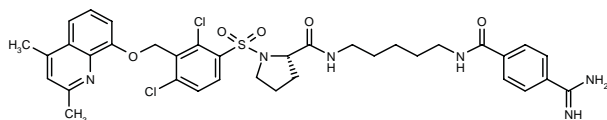
SOURCES – Adolor; University of California, San Diego, CA (US).

REFERENCES

1. Shreder, K. et al. *Synthesis and biological activity of a novel methylamine-bridged enkephalin analogue (MABE): A new route to cyclic peptides and peptidomimetics*. J Med Chem 1998, 41(14): 2631.

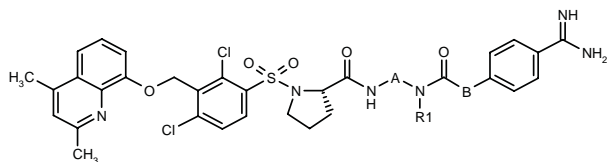
266223

N-[5-(4-Amidinobenzamido)pentyl]-1-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)phenylsulfonyl]-L-prolinamide



C36 H40 Cl2 N6 O5 S; Mol wt: 739.7210

ACTION – Agent for the treatment of pain and inflammation, a competitive bradykinin B_2 receptor antagonist (100% inhibition of [3 H]-bradykinin binding in guinea pig ileum preparations at 1 μ M). A representative compound from a series of *N*-benzenesulfonyl-L-proline derivatives, wherein the following are also included:



Compound	R1	A	B	Formula
267328	H	-(CH2)2-	bond	C ₃₃ H ₃₄ Cl ₂ N ₆ O ₅ S
267329	H	-(CH2)2-	-CH2O-	C ₃₄ H ₃₆ Cl ₂ N ₆ O ₆ S
267330	H	-(CH2)3-	bond	C ₃₄ H ₃₆ Cl ₂ N ₆ O ₅ S
267331	H	-(CH2)3-	-CH2-	C ₃₅ H ₃₈ Cl ₂ N ₆ O ₅ S
267332	H	-(CH2)3-	-CH2O-	C ₃₅ H ₃₈ Cl ₂ N ₆ O ₆ S
267333	Et	-(CH2)3-	bond	C ₃₆ H ₄₀ Cl ₂ N ₆ O ₅ S
267334	Me	-(CH2)3-	bond	C ₃₅ H ₃₈ Cl ₂ N ₆ O ₅ S
267335	H	-(CH2)4-	bond	C ₃₅ H ₃₈ Cl ₂ N ₆ O ₅ S

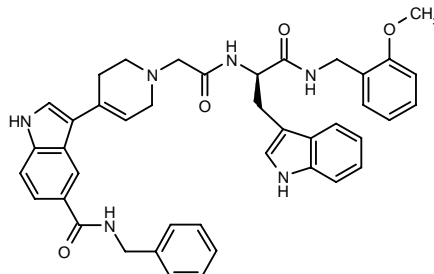
SOURCE – Fournier.

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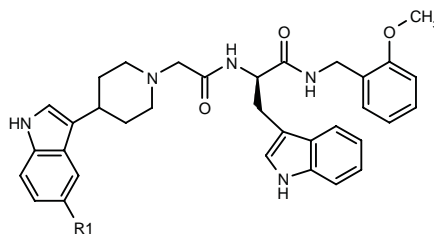
267387

*N*²-[2-[4-[5-(*N*-Benzylcarbamoyl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl]acetyl]-*N*¹-(2-methoxybenzyl)-D-tryptophanamide

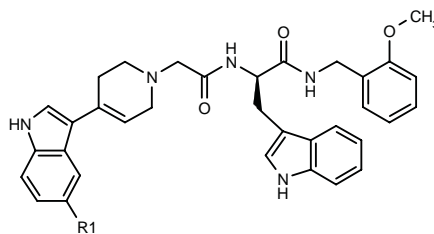


C42 H42 N6 O4; Mol wt: 694.8318

ACTION – Agent for the treatment of pain, migraine, the common cold, allergic rhinitis and CNS disorders such as anxiety with tachykinin receptor-antagonist and 5-HT receptor-agonist activity. A representative compound from a series of bisindole derivatives, wherein the following are also included:



Compound	R1	Formula
267388	OH	C ₃₄ H ₃₇ N ₅ O ₄
267391	F	C ₃₄ H ₃₆ FN ₅ O ₃
267392	Cl	C ₃₄ H ₃₆ ClN ₅ O ₃
267393	4-F-PhCONH	C ₄₁ H ₄₁ FN ₆ O ₄



Compound	R1	Formula
267389	F	C ₃₄ H ₃₄ FN ₅ O ₃
267390	OMe	C ₃₅ H ₃₇ N ₅ O ₄
267394	CN	C ₃₅ H ₃₄ N ₆ O ₃
267395	Cl	C ₃₄ H ₃₄ ClN ₅ O ₃

SOURCE – Lilly.

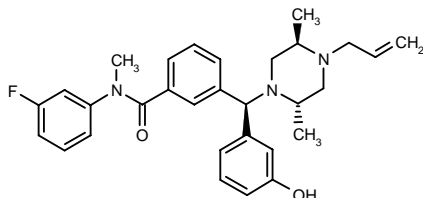
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DPI-3290*

220844

(+)-3-[1(*R*)-[4-Allyl-2(*S*),5(*R*)-dimethylpiperazin-1-yl]-1-(3-hydroxyphenyl)methyl]-*N*-(3-fluorophenyl)-*N*-methylbenzamide



C30 H34 F N3 O2; Mol wt: 487.6156

ACTION – Opioid analgesic agent with potent agonist effects at both δ - and μ -opioid receptors, as demonstrated in binding (IC_{50} = 1.5 and 2.5 nM, respectively, for δ - and μ -opioid receptors) and in functional studies (ED_{50} = 0.79 and 3.4 nM, respectively, in the mouse vas deferens and guinea pig ileum). DPI-3290 exhibited a significantly greater separation between antinociceptive doses in the rat tail-pinch test and doses causing respiratory depression than fentanyl or morphine.

SOURCES – Delta Pharmaceuticals; Glaxo Wellcome.

REFERENCES

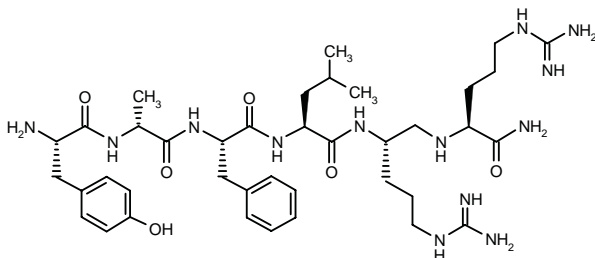
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3. Bishop, M.J. et al. *DPI3290: A mixed δ/μ opioid agonist analgesic with reduced side effects*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 294.

*Identified compound **220844** Drug Data Report 1995, 017(07): 0599.

SK-9709

266150

L-Tyrosyl-D-alanyl-L-phenylalanyl-L-leucyl-L-arginyl- $\psi(CH_2NH)$ -L-argininamide



C39 H63 N13 O6; Mol wt: 810.0117

ACTION – Antinociceptive agent, a dynorphin analog with activity in the acetic acid-induced writhing test in mice (ED_{50} = 1.36 μ mol/kg s.c., 2.11 nmol/mouse intracerebroventricularly and 0.79 nmol/mouse intrathecally), effects that could be reversed by the opioid receptor antagonist naloxone, the selective μ -opioid receptor antagonist β -funaltrexamine and the κ -opioid receptor antagonist nor-binaltorphimine. In the hot-plate test in mice, SK-9709 was half as potent as morphine following s.c. administration.

Its antinociceptive effects appear to be mediated by both supraspinal μ - and spinal κ -opioid receptors.

SOURCES – Meijo University, Nagoya (JP); Tohoku College of Pharmacy, Sendai (JP).

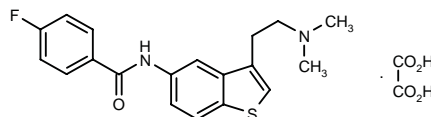
REFERENCES

1. Inoue, K. et al. *Antinociceptive effects of a novel dynorphin analog, Tyr-D-Ala-Phe-Leu-Arg $\psi(CH_2NH)$ Arg-NH₂*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.100.

ANTIMIGRAINE DRUGS

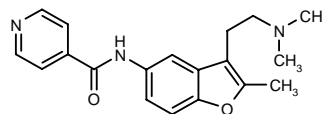
264432

N-[3-[2-(Dimethylamino)ethyl]benzo[*b*]thien-5-yl]-4-fluorobenzamide oxalate



C19 H19 F N2 O S . C2 H2 O4; Mol wt: 432.4699

ACTION – Agent for the treatment of migraine and associated disorders, a 5-HT_{1F} receptor agonist. A representative compound from a series of bicyclic derivatives, wherein the following is also included:



267736: C19 H21 N3 O2

SOURCE – Lilly.

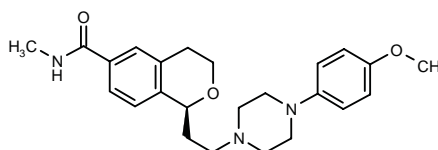
REFERENCES

1. Fritz, J.E. et al. (Eli Lilly and Company) *New serotonin 5-HT_{1F} agonists*. EP 835869, US 5792763, WO 9815545.

PNU-109291

265669

(-)-1(*S*)-[2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl]-*N*-methyl-3,4-dihydro-1*H*-2-benzopyran-6-carboxamide



C24 H31 N3 O3; Mol wt: 409.5269

ACTION – Antimigraine agent, one of the most potent and selective 5-HT_{1D} receptor agonists reported to date (K_i = 0.9 nM vs. 5775 nM for 5-HT_{1B} receptors) with additional weak affinity for 5-HT_{2A} (K_i = 168 nM) and dopamine D₂ receptors (K_i = 241 nM). Its strong hypothermic effects in guinea pigs indicated good blood–brain barrier penetration. The compound was significantly more potent than sumatriptan in blocking neurogenic inflammation in guinea pigs, with nearly complete inhibition of plasma extravasation at a dose of 1.0 µg/kg i.v. (300 µg/kg i.v. for sumatriptan). In contrast to sumatriptan, it showed no vasoconstrictive effect in cat carotid artery, indicating that it may be free of the cardiovascular side effects associated with sumatriptan. Compound displayed excellent oral bioavailability in rats (70 ± 20%).

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Ennis, M.D. and Tenbrink, R.E. (Pharmacia AB) *1,6-Disubstd. isochromans for treatment of migraine headaches*. EP 836599, WO 9702259.

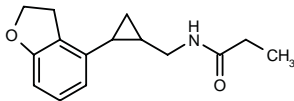
2. Ennis, M.D. et al. *Isochroman-6-carboxamides as highly selective 5-HT_{1D} agonists: Potential new treatment for migraine without cardiovascular side effects*. J Med Chem 1998, 41(13): 2180.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

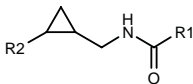
267635

N-[2-(2,3-Dihydrobenzofuran-4-yl)cyclopropylmethyl]-propionamide



C15 H19 N O2; Mol wt: 245.3201

ACTION – Melatonin agonist (IC_{50} < 10 nM against 2-[¹²⁵I]-iodomelatonin binding to human melatonin mt₁ (MEL_{1A}) receptors expressed in NIH-3T3 cells) potentially useful for the treatment of sleep and circadian rhythm disorders. Other compounds from this series of substituted benzodioxoles, benzofurans, dihydrobenzofurans and benzodioxanes include the following:



Compound	R1	R2	Formula
267636	Me	1,3-benzodioxol-4-yl	C ₁₃ H ₁₅ NO ₃
267637	Et	4-benzofuryl	C ₁₅ H ₁₇ NO ₂
267639	Pr	2,3-dihydro-4-benzofuryl	C ₁₆ H ₂₁ NO ₂
267640	vinyl	1,4-benzodioxan-5-yl	C ₁₅ H ₁₇ NO ₃
267641	CF3	1,4-benzodioxan-5-yl	C ₁₄ H ₁₄ F ₃ NO ₃
267642	Pr	2-Me-4-benzofuryl	C ₁₇ H ₂₁ NO ₂
267643	Et	2-Me-2,3-dihydro-4-benzofuryl	C ₁₈ H ₂₃ NO ₂
267645	Et	3,4-dihydro-2H-5-benzopyranyl	C ₁₆ H ₂₁ NO ₂

SOURCE – Bristol-Myers Squibb.

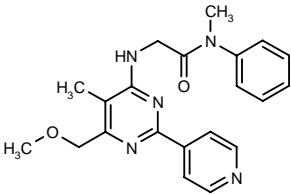
REFERENCES

1. Catt, J.D. et al. (Bristol-Myers Squibb Co.) *Benzodioxole, benzofuran, dihydrobenzofuran, and benzodioxane melatonergic agents*. WO 9825606.

ANXIOLYTICS

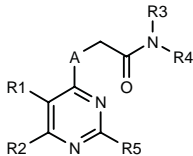
263802

2-[6-(Methoxymethyl)-5-methyl-2-(4-pyridyl)pyrimidin-4-ylamino]-N-methyl-N-phenylacetamide



C21 H23 N5 O2; Mol wt: 377.4457

ACTION – Anxiolytic agent that acts selectively at the ω₃ subunit of BZ site of the GABA_A receptor (IC_{50} = 6.5 nM vs. IC_{50} > 1000 nM for ω₁ and ω₂ subunits). Anxiolytic activity was demonstrated in a light–dark box test in mice, where compound exhibited a minimum effective dose (MED) of 0.01 mg/kg p.o. Other compounds from this series of 2,4-disubstituted pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
267348	Me	Me	Pr	Pr	2-thienyl	NH	C ₁₈ H ₂₆ N ₄ O ₅
267349	H	NHMe	Ph	Me	4-Pyr	NH	C ₁₉ H ₂₀ N ₆ O
267350	Me	OMe	4-MeO-Ph	Me	3-Pyr	NH	C ₂₁ H ₂₃ N ₅ O ₃
267351	Me	Me	Ph	Et	4-Pyr	O	C ₂₁ H ₂₂ N ₄ O ₂
267352	Me	Me	Pr	Pr	3-Pyr	O	C ₁₉ H ₂₆ N ₄ O ₂

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Murata, T. et al. (Dainippon Pharmaceutical Co., Ltd.) *2,4-Disubstd. pyrimidine derivs., process for producing the same, and medicinal compsns. containing the same*. WO 9809960.

ACTION – Antimigraine agent, one of the most potent and selective 5-HT_{1D} receptor agonists reported to date (K_i = 0.9 nM vs. 5775 nM for 5-HT_{1B} receptors) with additional weak affinity for 5-HT_{2A} (K_i = 168 nM) and dopamine D₂ receptors (K_i = 241 nM). Its strong hypothermic effects in guinea pigs indicated good blood–brain barrier penetration. The compound was significantly more potent than sumatriptan in blocking neurogenic inflammation in guinea pigs, with nearly complete inhibition of plasma extravasation at a dose of 1.0 µg/kg i.v. (300 µg/kg i.v. for sumatriptan). In contrast to sumatriptan, it showed no vasoconstrictive effect in cat carotid artery, indicating that it may be free of the cardiovascular side effects associated with sumatriptan. Compound displayed excellent oral bioavailability in rats (70 ± 20%).

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Ennis, M.D. and Tenbrink, R.E. (Pharmacia AB) *1,6-Disubstd. isochromans for treatment of migraine headaches*. EP 836599, WO 9702259.

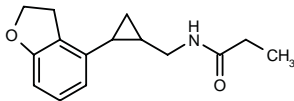
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

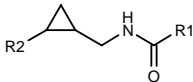
267635

N-[2-(2,3-Dihydrobenzofuran-4-yl)cyclopropylmethyl]-propionamide



C15 H19 N O2; Mol wt: 245.3201

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267641	CF3	1,4-benzodioxan-5-yl	C ₁₄ H ₁₄ F ₃ NO ₃
267642	Pr	2-Me-4-benzofuryl	C ₁₇ H ₂₁ NO ₂
267643	Et	2-Me-2,3-dihydro-4-benzofuryl	C ₁₈ H ₂₃ NO ₂
267645	Et	3,4-dihydro-2H-5-benzopyranyl	C ₁₆ H ₂₁ NO ₂

SOURCE – Bristol-Myers Squibb.

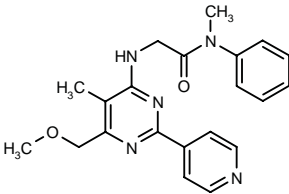
REFERENCES

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ANXIOLYTICS

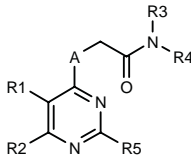
263802

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C21 H23 N5 O2; Mol wt: 377.4457

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Compound	R1	R2	R3	R4	R5	A	Formula
267348	Me	Me	Pr	Pr	2-thienyl	NH	C ₁₈ H ₂₆ N ₄ O ₅
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267350	Me	OMe	4-MeO-Ph	Me	3-Pyr	NH	C ₂₁ H ₂₃ N ₅ O ₃
267351	Me	Me	Ph	Et	4-Pyr	O	C ₂₁ H ₂₂ N ₄ O ₂
267352	Me	Me	Pr	Pr	3-Pyr	O	C ₁₉ H ₂₆ N ₄ O ₂

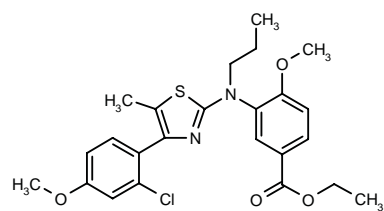
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Murata, T. et al. (Dainippon Pharmaceutical Co., Ltd.) *2,4-Disubstd. pyrimidine derivs., process for producing the same, and medicinal compsns. containing the same*. WO 9809960.

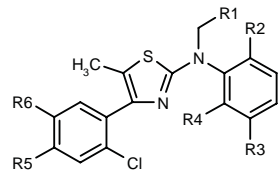
264431

3-[N-[4-(2-Chloro-4-methoxyphenyl)-5-methylthiazol-2-yl]-N-propylamino]-4-methoxybenzoic acid ethyl ester



C24 H27 Cl N2 O4 S; Mol wt: 475.0063

ACTION – Agent for the treatment of stress-related disorders, anxiety, depression, anorexia nervosa, sexual and fertility disorders and Alzheimer’s disease, a corticotropin-releasing factor (CRF) antagonist. Within this series of specifically claimed aminothiazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
267672	Et	Cl	H	Cl	OMe	H	C ₂₀ H ₁₉ Cl ₃ N ₂ OS
267673	Et	Cl	CF ₃	H	OMe	H	C ₂₁ H ₁₉ Cl ₂ F ₃ N ₂ OS
267674	Et	Me	H	OMe	Cl	H	C ₂₁ H ₂₂ Cl ₂ N ₂ OS
267675	Et	OMe	NO ₂	H	OMe	H	C ₂₁ H ₂₂ ClN ₃ O ₄ S
267676	Et	Me	Cl	H	Cl	H	C ₂₀ H ₁₉ Cl ₃ N ₂ S
267677	Et	OMe	Me	H	OMe	Me	C ₂₃ H ₂₇ ClN ₂ O ₂ S
267678	ethynyl	Me	Cl	H	OMe	Me	C ₂₂ H ₂₀ Cl ₂ N ₂ OS

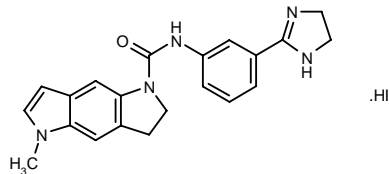
SOURCE – Sanofi.

REFERENCES

1. Fontaine, E. et al. (Sanofi) *Aminothiazole derivs., method of preparation and pharmaceutical compns. containing same.* WO 9815543.

267449

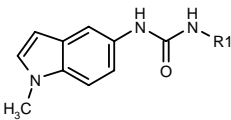
N-[3-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-5-methyl-1,2,3,5-tetrahydropyrrolo[2,3-f]indole-1-carboxamide hydroiodide



C21 H21 N5 O . HI; Mol wt: 487.3388

ACTION – Agent for the treatment of CNS disorders such as anxiety, depression, obsessive–compulsive disorders, migraine, anorexia, bulimia, Alzheimer’s disease, sleep disorders, panic attacks, drug and alcohol withdrawal symptoms and disorders associated with spinal trauma and/or head injury with 5-HT_{2C} receptor-antagonist activity (97% inhibition of [³H]-mesulergine binding in rat prefrontal cortex preparations at 10 μM). Other

compounds from this series of indole urea derivatives include the following:



Compound	R1	Formula
267450	5-(5-Me-3-pyrazolyl)-3-Pyr	C ₁₉ H ₁₈ N ₆ O
267451	3-(1-imidazolyl)-Ph	C ₁₉ H ₁₇ N ₅ O

SOURCE – Fujisawa.

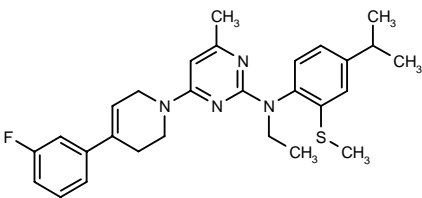
REFERENCES

1. Ito, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Indole-urea derivs. with 5-HT antagonist properties.* WO 9824785.

CRA-1000¹⁻⁶

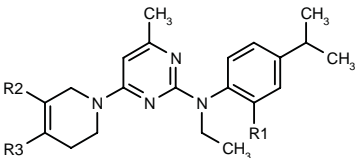
267151

N-Ethyl-4-[4-(3-fluorophenyl)-1,2,3,6-tetrahydro-1-pyridin-yl]-N-[4-isopropyl-2-(methylsulfanyl)phenyl]-6-methylpyrimidin-2-amine



C28 H33 F N4 S; Mol wt: 476.6607

ACTION – High-affinity and selective, nonpeptide corticotropin-releasing factor (CRF) CRF₁ receptor antagonist (IC₅₀ = 10.5 nM; IC₅₀ CRF_{2α} > 1000 nM) proven to ameliorate stress- and CRF-induced anxiogenic-like behaviors in rats with minimal effective doses of 0.3-10 mg/kg p.o., while having no effect on spontaneous locomotor activity in mice, hexobarbital-induced anesthesia in mice or on a passive avoidance task in rats. Potentially useful in the treatment of depression and anxiety-related disorders. Other compounds from this series of aryl-1,2,3,6-tetrahydro-pyridinopyrimidine derivatives include the following:



Compound	R1	R2	R3	Formula
CRA-0165 [267152] ^{1,3-5}	SMe	2-Me-Ph	H	C ₂₉ H ₃₈ N ₄ S
CRA-1001 [267153] ¹⁻⁶	Br	H	3-F-Ph	C ₂₇ H ₃₀ BrFN ₄

SOURCE – Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *4-Tetrahydropyridylpyrimidine derivs.* WO 9842699.
2. Chaki, S. et al. *Neuropharmacological profile of non-peptide CRF1 antagonist, CRA100 and CRA1001.* Soc Neurosci Abst 1998, 24(Part 1): Abst 234.1.

3. Nakazato, A. et al. *Aryl-1,2,3,6-tetrahydropyridinopyrimidine derivatives as CRF1 receptor antagonists*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.101.

4. Nakazato, A. et al. *Aryl-1,2,3,6-tetrahydropyridinopyrimidine derivatives as CRF1 receptor antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 137.

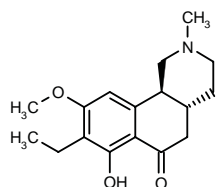
5. Nakazato, A. et al. *CRF1 receptor antagonists: Aryl-1,2,3,6-tetrahydropyridinopyrimidine derivatives*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-26.

6. Okuyama, S. et al. *Behavioral and electrophysiological profile of non-peptide CRF1 antagonists CRA1000 and CRA1001*. Soc Neurosci Abst 1998, 24(Part 1): Abst 234.2.

RO-60-0759

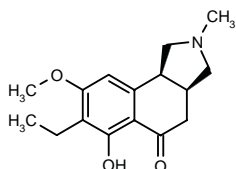
266973

(+)-*trans*-8-Ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydrobenzo[*h*]isoquinolin-6(2*H*)-one



C17 H23 N O3; Mol wt: 289.3727

ACTION – 5-HT_{2C} receptor antagonist or partial agonist derived from the natural antagonist *O*-methyl-asparvenone, with potent antagonist activity against mCPP-induced penile erections in rats (ID₅₀ = 10 mg/kg p.o., 2.5 mg/kg s.c.). Another related compound is:



Ro-60-0869 [266974]: C16 H21 N O3

5-HT_{2C} receptor antagonists are expected to have therapeutic potential in the treatment of anxiety, sleep disorders and migraine.

SOURCE – Roche.

REFERENCES

1. Bös, M. et al. (F. Hoffmann-La Roche AG) *Tricyclic benzo[e]isoindoles and benzo[h]isoquinolines*. WO 9830546.

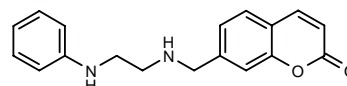
2. Bös, M. et al. *Syntheses of novel 5-HT_{2C} receptor ligands derived from O-methylasparvenone, a nitrogen-free serotonin antagonist*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 027.

ANTIPSYCHOTIC DRUGS

PD-165167

267068

7-[*N*-[2-(Phenylamino)ethyl]aminomethyl]-2*H*-[1]-benzopyran-2-one



C18 H18 N2 O2; Mol wt: 294.3522

ACTION – Antipsychotic agent apparently devoid of extrapyramidal side effects, a potent and selective dopamine D₄ receptor antagonist, as shown in binding studies by K_i values of 5.8, 424 and 2920 nM, respectively, for D₄, D₃ and D₂ receptors and values > 2000 nM against α₁- or α₂-adrenoceptors, 5-HT_{1A} and 5-HT₂ receptors; PD-165167 inhibited the increase in [³H]-thymidine uptake induced by quinpirole *in vitro* (IC₅₀ = 1.3 nM), with no agonist activity. It was active orally in animal models predictive of antipsychotic efficacy such as the prepulse acoustic startle test in rats (30 mg/kg), but it exhibited no effect on spontaneous locomotor activity in rodents and did not induce catalepsy in rats at a dose of 10 mg/kg p.o.

SOURCE – Warner-Lambert.

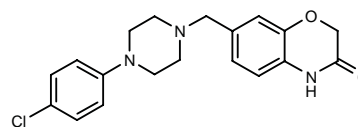
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1. Kesten, S.R. et al. *Design, synthesis, and evaluation of coumarins as potent and selective dopamine D₄ antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 123.

PD-172760

266873

7-[4-(4-Chlorophenyl)-1-piperazinylmethyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-one



C19 H20 Cl N3 O2; Mol wt: 357.8390

ACTION – Antipsychotic agent with high affinity and selectivity for dopamine D₄ receptors (K_i = 4.3 nM; D₄/D₂ = 100), reported to have good activity in animal behavioral models indicative of antipsychotic activity in humans.

SOURCE – Warner-Lambert.

REFERENCES

1. Belliotti, T. et al. (Warner-Lambert Co.) *Benzoxazinone dopamine D₄ receptor antagonists*. WO 9745419.

2. Belliotti, T.R. et al. *PD 172760. A potential new antipsychotic agent*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 028.

3. Corbin, A.E. et al. *Effects of the novel dopamine (DA) D₄ receptor antagonist PD 172760 in preclinical behavioral models of antipsychotic activity in rodents*. Soc Neurosci Abst 1998, 24(Part 2): Abst 682.6.

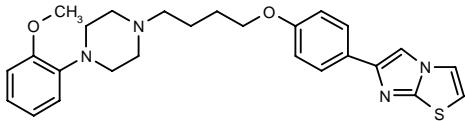
4. Georgic, L.M. et al. *Neurochemical profile of PD 172760 (7-[4-(4-chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one), a novel high affinity antagonist at the human dopamine D4 receptor.* Soc Neurosci Abst 1998, 24(Part 2): Abst 682.8.

5. Wustrow, D.J. et al. *Benzoxazinone dopamine D4 receptor antagonists: Structure activity relationships.* Soc Neurosci Abst 1998, 24(Part 2): Abst 682.7.

RGH-1756

266148

6-[4-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butoxy]-phenyl]imidazo[2,1-b]thiazole



C26 H30 N4 O2 S; Mol wt: 462.6150

ACTION – Atypical antipsychotic agent that appears to be effective against both positive and negative symptoms and cognitive disturbances of schizophrenia, and to have a low liability for extrapyramidal side effects. It displays strong affinity for human dopamine D₃ (IC₅₀ = 0.2 nM) receptors, as well as 5-HT_{1A} (IC₅₀ = 8 nM), D_{2L} receptors (IC₅₀ = 10 nM) and α₁-adrenoceptors (IC₅₀ = 28 nM), with 40-fold selectivity over D₂ receptors and much lower or no affinity for a range of other receptors. It antagonized apomorphine-induced climbing in mice (ED₅₀ = 6.1 mg/kg p.o. and 0.7 mg/kg s.c.), whereas it was much less active against apomorphine-induced stereotyped sniffing (ED₅₀ > 30 mg/kg p.o. and 6 mg/kg s.c.), indicating good limbic selectivity. Compound also antagonized apomorphine-, amphetamine- and phencyclidine-induced hyperlocomotion in rats at 1-10 mg/kg p.o., whereas spontaneous locomotion was inhibited only at a dose of 30 mg/kg p.o. Cataleptogenic activity was observed only at relatively high doses (ED₅₀ = 78 mg/kg p.o. in mice and > 100 mg/kg p.o. in rats). Retrograde and anterograde amnesia in a passive avoidance test in mice was prevented by RGH-1756, and it also exhibited anxiolytic-like effects in the elevated plus-maze in rats at 1 mg/kg p.o.

SOURCE – Gedeon Richter.

REFERENCES

1. Laszlovsky, I. et al. (Gedeon Richter) *2-Methoxyphenylpiperazine derivs.* WO 9818797.

2. Kiss, B. et al. *RGH-1756, a new potential atypical antipsychotic: Effects on central monoaminergic neurotransmission.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.124.

3. Laszlovsky, I. et al. *New potential atypical antipsychotic with unusual pharmacological profile.* Naunyn-Schmied Arch Pharmacol 1997, 356(4, Suppl. 1): Abst 124.

4. Laszlovsky, I. et al. *RGH-1756, a new potential atypical antipsychotic: Anatomical mapping of potential targets.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.122.

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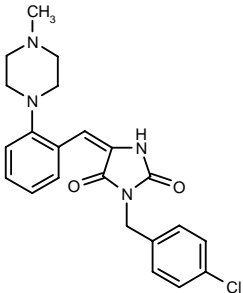
7. Szabo, S. et al. *RGH-1756, a new potential atypical antipsychotic: Learning and memory profile.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.13.

8. Terj ki, E. et al. *RGH-1756, a new potential atypical antipsychotic: Pharmacokinetic data.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 2.10.

ANTIDEPRESSANTS

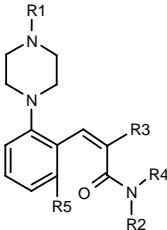
264408

3-(4-Chlorobenzyl)-5-[2-(4-methylpiperazin-1-yl)benzylidene]imidazolidine-2,4-dione

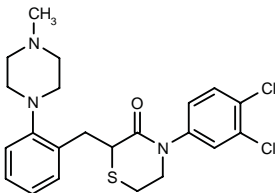


C22 H23 Cl N4 O2; Mol wt: 410.9027

ACTION – Agent for the treatment of depression, anxiety, sexual dysfunction, eating disorders, migraine, pain, hypertension, Alzheimer’s disease and Parkinson’s disease with affinity for 5-HT_{1A} and/or 5-HT_{1D} receptors. A representative compound from a series of heterocyclic lactams, wherein the following are also specifically claimed:



Compound	R1	R2	R3,R4	R5	Formula
266805	Me	4-Cl-Ph	-NHCO-	H	C ₂₁ H ₂₁ ClN ₄ O ₂
266806	Me	4-Cl-PhCH2	-SCO-	H	C ₂₂ H ₂₂ ClN ₄ O ₂ S
266807	Me	CH2Ph	-SCH2CH2-	H	C ₂₃ H ₂₇ N ₃ OS
266808	Me	3,4-(Cl)2-PhCH2	-SCH2CH2-	H	C ₂₃ H ₂₅ Cl ₂ N ₃ OS
266809	Me	4-Cl-Ph	-SCO-	H	C ₂₁ H ₂₀ ClN ₃ O ₂ S
266810	Me	4-CF3-Ph	-SCO-	H	C ₂₂ H ₂₀ F ₃ N ₃ O ₂ S
266811	Me	4-CF3-Ph	-SCH2CH2-	H	C ₂₃ H ₂₄ F ₃ N ₃ OS
266812	Me	H	-SCH2CH2-	H	C ₁₆ H ₂₁ N ₃ OS
266813	Me	3,4-(Cl)2-Ph	-SCH2CH2-	F	C ₂₂ H ₂₂ Cl ₂ FN ₃ OS
266814	Me	3,4-(Cl)2-Ph	-OCH2CH2-	H	C ₂₂ H ₂₃ Cl ₂ N ₃ O ₂
266815	Me	3,4-(Cl)2-Ph	-SCH2CH2-	H	C ₂₂ H ₂₃ Cl ₂ N ₃ OS
266817	Me	Me	-SCH2CH2-	H	C ₁₇ H ₂₃ N ₃ OS
266818	H	3,4-(Cl)2-Ph	-SCH2CH2-	H	C ₂₁ H ₂₁ Cl ₂ N ₃ OS



266816: C22 H25 Cl2 N3 OS

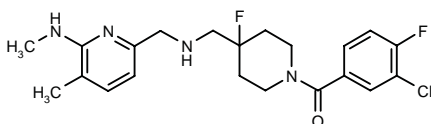
SOURCE – Pfizer.

REFERENCES

1. Howard, H.R. (Pfizer Inc.) *Aralkyl and aralkylidene heterocyclic lactams and imides*. WO 9814433.

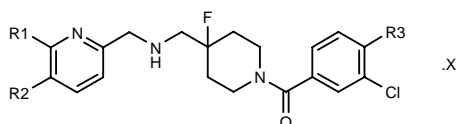
265523

1-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-[5-methyl-6-(methylamino)pyridin-2-ylmethylaminomethyl]piperidine



C21 H25 Cl F2 N4 O; Mol wt: 422.9045

ACTION – Highly potent and selective 5-HT_{1A} receptor agonist ($pK_i = 10.12$) with 16,982-fold selectivity relative to dopamine D₂ receptors ($pK_i = 5.89$), showing improved potency and selectivity compared to buspirone (pK_i 5-HT_{1A} = 7.65, pK_i D₂ = 7.49, ratio = 1.5) and 8-OH-DPAT (pK_i 5-HT_{1A} = 8.85, pK_i D₂ = 6.26, ratio = 389) and therefore expected to cause fewer side effects than the reference compounds. 5-HT_{1A} receptor-agonist activity was assessed *in vivo* by measuring lower lip retraction in rats upon p.o. administration ($ED_{50} = 0.08$ mg/kg p.o. vs. 20 and 5 mg/kg p.o. for buspirone and 8-OH-DPAT, respectively). Potentially useful for the treatment of depression, anxiety, obsessive–compulsive disorder, panic attacks, pain, aggression, alcohol abuse, sleep disturbances, cerebrovascular disorders, migraine and vomiting. Within this series of pyridin-2-ylmethylamine derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
266549	N(Me)2	H	F		C ₂₁ H ₂₅ ClF ₂ N ₄ O
266550	1-azetidinyI	H	F	oxalate	C ₂₂ H ₂₅ ClF ₂ N ₄ O .C ₂ H ₂ O ₄
266551	NHEt	H	F	oxalate	C ₂₁ H ₂₅ ClF ₂ N ₄ O .C ₂ H ₂ O ₄
266552	NHMe	H	F	fumarate	C ₂₀ H ₂₃ ClF ₂ N ₄ O .C ₄ H ₄ O ₄
266553	NHMe	H	Cl	fumarate	C ₂₀ H ₂₃ Cl ₂ FN ₄ O .C ₄ H ₄ O ₄
266554	N(Me)2	H	Cl		C ₂₁ H ₂₅ Cl ₂ FN ₄ O
266555	2-furyl	H	F		C ₂₃ H ₂₂ ClF ₂ N ₃ O ₂
266556	N(Me)2	Me	F		C ₂₂ H ₂₇ ClF ₂ N ₄ O
266557	3-pyrazolyl	H	F	oxalate	C ₂₂ H ₂₂ ClF ₂ N ₅ O .C ₂ H ₂ O ₄
266558	H	Me	Cl	fumarate	C ₂₀ H ₂₂ Cl ₂ FN ₃ O .C ₄ H ₄ O ₄

SOURCE – Pierre Fabre.

REFERENCES

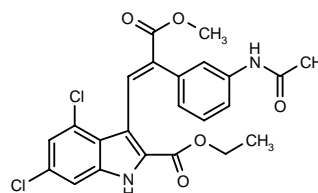
1. Vacher, B. et al. (Pierre Fabre Médicament) *Pyridin-2-yl-methylamine derivs., method of preparing and application as medicine*. WO 9822459.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

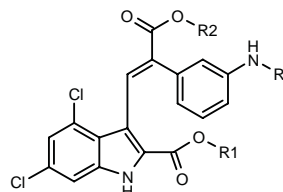
264404

2-(3-Acetamidophenyl)-3-[4,6-dichloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl]-2(*E*)-propenoic acid methyl ester



C₂₃ H₂₀ Cl₂ N₂ O₅; Mol wt: 475.3260

ACTION – Excitatory amino acid antagonist that preferentially binds to the strychnine-insensitive glycine binding site on the NMDA receptor complex, potentially useful as an anticonvulsant and antiischemic agent, as well as for the treatment of neurodegenerative disorders, anxiety, pain and migraine. Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	Formula
266825	Et	Me	COPh	C ₂₈ H ₂₂ Cl ₂ N ₂ O ₅
266826	Et	Me	CO ₂ Me	C ₂₃ H ₂₀ Cl ₂ N ₂ O ₆
266827	Et	Me	CO ₂ Et	C ₂₄ H ₂₂ Cl ₂ N ₂ O ₆
266828	Et	Me	i-PrOCO	C ₂₅ H ₂₄ Cl ₂ N ₂ O ₆
266829	Et	Me	SO ₂ Me	C ₂₂ H ₂₀ Cl ₂ N ₂ O ₆ S
266830	H	H	Ac	C ₂₀ H ₁₄ Cl ₂ N ₂ O ₅
266831	H	H	COPh	C ₂₆ H ₁₆ Cl ₂ N ₂ O ₅

SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Harrison, B.L. et al. (Hoechst Marion Roussel, Inc.) *NMDA (N-methyl-D-aspartate) antagonists*. WO 9814427.

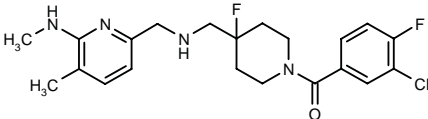
SOURCE – Pfizer.

REFERENCES

1. Howard, H.R. (Pfizer Inc.) *Aralkyl and aralkylidene heterocyclic lactams and imides*. WO 9814433.

265523

1-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-[5-methyl-6-(methylamino)pyridin-2-ylmethylaminomethyl]piperidine



C21 H25 Cl F2 N4 O; Mol wt: 422.9045

ACTION – Highly potent and selective 5-HT_{1A} receptor agonist (pK_i = 10.12) with 16,982-fold selectivity relative to dopamine D₂ receptors (pK_i = 5.89), showing improved potency and selectivity compared to buspirone (pK_i 5-HT_{1A} = 7.65, pK_i D₂ = 7.49, ratio = 1.5) and 8-OH-DPAT (pK_i 5-HT_{1A} = 8.85, pK_i D₂ = 6.26, ratio = 389) and therefore expected to cause fewer side effects than the reference compounds. 5-HT_{1A} receptor-agonist activity was assessed *in vivo* by measuring lower lip retraction in rats upon p.o. administration (ED₅₀ = 0.08 mg/kg p.o. vs. 20 and 5 mg/kg p.o. for buspirone and 8-OH-DPAT, respectively). Potentially useful for the treatment of depression, anxiety, obsessive–compulsive disorder, panic attacks, pain, aggression, alcohol abuse, sleep disturbances, cerebrovascular disorders, migraine and vomiting. Within this series of pyridin-2-ylmethylamine derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
266549	N(Me)2	H	F		C ₂₁ H ₂₅ ClF ₂ N ₄ O
266550	1-azetidinyI	H	F	oxalate	C ₂₂ H ₂₅ ClF ₂ N ₄ O .C ₂ H ₂ O ₄
266551	NHEt	H	F	oxalate	C ₂₁ H ₂₅ ClF ₂ N ₄ O .C ₂ H ₂ O ₄
266552	NHMe	H	F	fumarate	C ₂₀ H ₂₃ ClF ₂ N ₄ O .C ₄ H ₄ O ₄
266553	NHMe	H	Cl	fumarate	C ₂₀ H ₂₃ Cl ₂ FN ₄ O .C ₄ H ₄ O ₄
266554	N(Me)2	H	Cl		C ₂₁ H ₂₅ Cl ₂ FN ₄ O
266555	2-furyl	H	F		C ₂₃ H ₂₂ ClF ₂ N ₃ O ₂
266556	N(Me)2	Me	F		C ₂₂ H ₂₇ ClF ₂ N ₄ O
266557	3-pyrazolyl	H	F	oxalate	C ₂₂ H ₂₂ ClF ₂ N ₅ O .C ₂ H ₂ O ₄
266558	H	Me	Cl	fumarate	C ₂₀ H ₂₂ Cl ₂ FN ₃ O .C ₄ H ₄ O ₄

SOURCE – Pierre Fabre.

REFERENCES

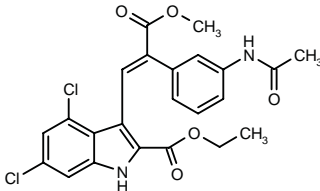
1. Vacher, B. et al. (Pierre Fabre Médicament) *Pyridin-2-yl-methylamine derivs., method of preparing and application as medicine*. WO 9822459.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

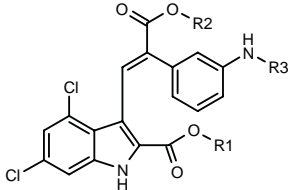
264404

2-(3-Acetamidophenyl)-3-[4,6-dichloro-2-(ethoxy-carbonyl)-1*H*-indol-3-yl]-2(*E*)-propenoic acid methyl ester



C23 H20 Cl2 N2 O5; Mol wt: 475.3260

ACTION – Excitatory amino acid antagonist that preferentially binds to the strychnine-insensitive glycine binding site on the NMDA receptor complex, potentially useful as an anticonvulsant and antiischemic agent, as well as for the treatment of neurodegenerative disorders, anxiety, pain and migraine. Other specifically claimed compounds from this series of indole derivatives include the following:



Compound	R1	R2	R3	Formula
266825	Et	Me	COPh	C ₂₈ H ₂₂ Cl ₂ N ₂ O ₅
266826	Et	Me	CO2Me	C ₂₃ H ₂₀ Cl ₂ N ₂ O ₆
266827	Et	Me	CO2Et	C ₂₄ H ₂₂ Cl ₂ N ₂ O ₆
266828	Et	Me	i-PrOCO	C ₂₅ H ₂₄ Cl ₂ N ₂ O ₆
266829	Et	Me	SO2Me	C ₂₂ H ₂₀ Cl ₂ N ₂ O ₆ S
266830	H	H	Ac	C ₂₀ H ₁₄ Cl ₂ N ₂ O ₅
266831	H	H	COPh	C ₂₅ H ₁₆ Cl ₂ N ₂ O ₅

SOURCE – Hoechst Marion Roussel.

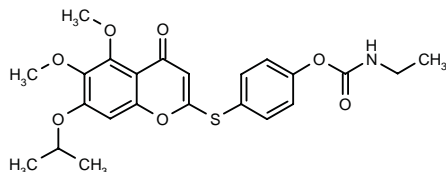
REFERENCES

1. Harrison, B.L. et al. (Hoechst Marion Roussel, Inc.) *NMDA (N-methyl-D-aspartate) antagonists*. WO 9814427.

COGNITION-ENHANCING DRUGS

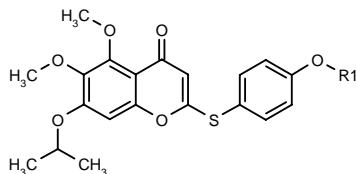
263846

N-Ethylcarbamic acid 4-(7-isopropoxy-5,6-dimethoxy-4-oxo-4*H*-1-benzopyran-2-ylsulfanyl)phenyl ester



C23 H25 N O7 S; Mol wt: 459.5165

ACTION – Neuroprotective agent for the treatment of neurodegenerative disorders such as Alzheimer's disease, Down's syndrome, Parkinson's disease, vascular dementia and amyotrophic lateral sclerosis that acts by inhibiting neuronal cell death. Compound shows good oral bioavailability in rats (67.38%) and it improves the sciatic nerve motor nerve conduction velocity in streptozotocin-induced diabetic rats following oral administration. Compound was found to inhibit phosphodiesterase derived from sciatic nerve with an IC_{50} value of 3.4 μ M. Within this series of chromone derivatives, the following are also included:



Compound	R1	Formula
267304	CH2SMe	C ₂₂ H ₂₄ O ₆ S ₂
267305	CO2Et	C ₂₃ H ₂₄ O ₆ S
267306	CON(Me) ₂	C ₂₃ H ₂₅ NO ₇ S
267307	CON(Me)CH ₂ CH ₂ OH	C ₂₄ H ₂₇ NO ₈ S

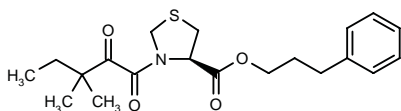
SOURCE – Tsumura.

REFERENCES

- Igarashi, Y. et al. (Tsumura & Co.) *Chromone derivs. and nerve cell death inhibitors containing the same*. WO 9811086.

264386

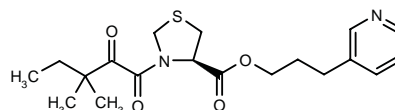
3-(3,3-Dimethyl-2-oxopentanoyl)thiazolidine-4(*R*)-carboxylic acid 3-phenylpropyl ester



C20 H27 N O4 S; Mol wt: 377.5023

ACTION – Low-molecular-weight neurotrophic agent with affinity for FKBP (FK-506-binding protein)-type immunophilins such as FKBP12 that inhibits peptidylprolyl isomerase (rotamase; K_i = 215 nM) and is devoid of immunosuppressive activity. *In vitro*, compound was

shown to stimulate immunophilin-induced neurite outgrowth in chick dorsal root ganglia (EC_{50} = 0.031 nM). Potentially useful for the treatment of neurological disorders such as peripheral neuropathies and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Another specifically claimed compound from this series of heterocyclic esters and amides is:



267027: C19 H26 N2 O4 S

SOURCE – Guilford.

REFERENCES

- Li, J.-H. and Hamilton, G.S. (Guilford Pharmaceuticals Inc.) *Heterocyclic esters and amides*. US 5801187, WO 9813355.

264861

Brain-associated inhibitor of tissue-type plasminogen activator

BAIT

ACTION – Polypeptide from the serine protease inhibitor (serpin) superfamily that is expressed primarily in human brain tissue and has been shown to exhibit selective inhibition of tissue-type plasminogen activator (t-PA), with relatively little inhibition of trypsin, thrombin or urokinase-type plasminogen activator (u-PA). Compound is believed to be the human homolog of chicken neuroserpin, which plays an important role in the regulation of local extracellular proteolysis involved in the reorganization of the synaptic connectivity during development and synapse plasticity in the adult. It is thus expected to be of use in the diagnosis and treatment of a number of disorders of the central and peripheral nervous system including impaired learning and memory processes associated with Alzheimer's disease.

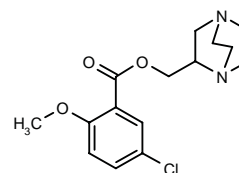
SOURCE – Human Genome Sciences.

REFERENCES

- Hastings, G.A. et al. (Human Genome Sciences, Inc.) *Brain-associated inhibitor of tissue-type plasminogen activator*. WO 9816643.

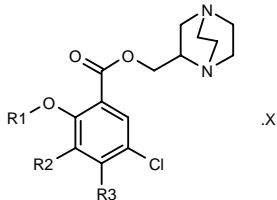
266226

5-Chloro-2-methoxybenzoic acid 1,4-diazabicyclo[2.2.2]-octan-2-ylmethyl ester



C15 H19 Cl N2 O3; Mol wt: 310.7791

ACTION – Agent for the treatment of CNS disorders such as cognitive disorders, psychoses, obsessive–compulsive disorders, depression and anxiety, as well as gastro-intestinal, cardiovascular and urinary disorders, with affinity for 5-HT₃ and/or 5-HT₄ receptors and which acts as a 5-HT₄ agonist and/or 5-HT₃ antagonist. Within this series of 1,4-diazabicyclo[2.2.2]oct-2-ylmethyl derivatives, the following are also included:



Compound	R1	R2	R3	X	Formula
267526	Me	H	NH2		C ₁₅ H ₂₀ ClN ₃ O ₃
267527	-(CH2)2-		H	HCl	C ₁₆ H ₁₉ ClN ₃ O ₃ .HCl
267528	-CH2CH2O-		NH2		C ₁₆ H ₂₀ ClN ₃ O ₄
267529	-(CH2)3O-		NH2	HCl	C ₁₇ H ₂₂ ClN ₃ O ₄ .HCl

SOURCE – Synthélabo.

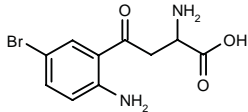
REFERENCES

1. Lochead, A. et al. (Synthélabo) *1,4-Diazabicyclo[2.2.2]oct-2-ylmethyl derivs., their preparation and therapeutic application.* WO 9824790.

FCE-28264

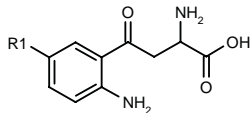
267228

2-Amino-4-(2-amino-5-bromophenyl)-4-oxobutyric acid



C10 H11 Br N2 O3; Mol wt: 287.1119

ACTION – Agent for the treatment of age-related cognition disorders and perinatal brain disorders that acts by inhibiting kynurenine aminotransferase (KAT), an enzyme that catalyzes the biosynthesis of kynurenic acid from kynurenine. At 100 μM, compound gave 52% inhibition of KAT activity in rat brain homogenates and 58% inhibition of kynurenic acid production in rat cortex slices. Other specifically claimed compounds from this series of substituted kynurenines include the following:



Compound	R1	Formula
FCE-28244 [267229]	Pr	C ₁₃ H ₁₈ N ₂ O ₃
FCE-28441 [267230]	i-Pr	C ₁₃ H ₁₈ N ₂ O ₃
FCE-28263 [267231]	cyclohexyl	C ₁₆ H ₂₂ N ₂ O ₃

SOURCES – University of Maryland, Baltimore, MD (US); Pharmacia & Upjohn.

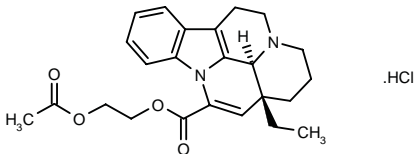
REFERENCES

1. Schwarcz, R. et al. (Pharmacia & Upjohn SpA;University of Maryland) *Subst. kynurenines and process for their preparation.* US 5786508, WO 9504714.

RGH-5279*

254084

(–)-(13a*R*,13b*S*)-13a-Ethyl-2,3,5,6,13a,13b-hexahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylic acid 2-acetoxyethyl ester hydrochloride



C24 H28 N2 O4 . HCl; Mol wt: 444.9561

ACTION – Orally active antiischemic and cognition-enhancing agent, a potent inhibitor of lipid peroxidation proven to significantly improve the ability of basal forebrain-lesioned rats to learn complex spatial tasks and to improve impaired learning, consolidation and retrieval in young rats. The compound appears to have potential particularly for improving impaired cognitive function caused by stroke or aging.

SOURCE – Gedeon Richter.

REFERENCES

1. Szántay, C. et al. (Gedeon Richter) *Trans apovincaminic acid ester derivs. as drugs.* EP 876367, WO 9723481.

2. Laszly, J. et al. *The effect of RGH-5279 on behavioral consequences of basal forebrain lesion in rats.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.121.

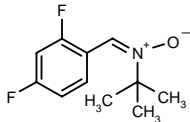
3. Paróczai, M. and Kápati, E. *Effect of RGH-5279 on learning and memory deficits of rats in water-labyrinth.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.120.

*Identified compound **254084** Drug Data Report 1997, 019(10): 0884.

TREATMENT OF
CEREBROVASCULAR DISEASES

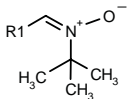
264378

N-*tert*-Butyl-*N*-(2,4-difluorobenzylidene)amine *N*-oxide

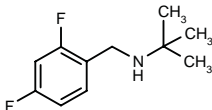


C11 H13 F2 N O; Mol wt: 213.2257

ACTION – Agent for the treatment of neurodegenerative disorders, a representative compound from a series of nitron derivatives, wherein the following are also included:



Compound	R1	Formula
267009	2,4-(Cl)2-Ph	C ₁₁ H ₁₃ Cl ₂ NO
267010	2-thienyl	C ₉ H ₁₃ NOS
267012	4-CF3-Ph	C ₁₂ H ₁₄ F ₃ NO
267013	4-Br-Ph	C ₁₁ H ₁₄ BrNO



267011: C₁₁ H₁₅ F₂ N

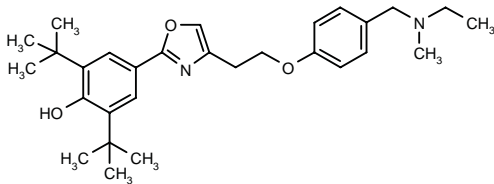
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Ikeda, K. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Nitrone derivs.* WO 9813332.

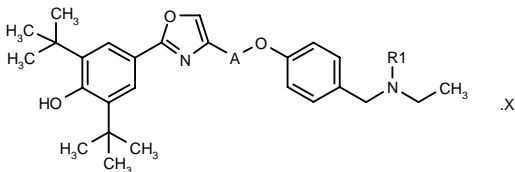
264423

2,6-Di-*tert*-butyl-4-[4-[2-[4-(*N*-ethyl-*N*-methylamino-methyl)phenoxy]ethyl]oxazol-2-yl]phenol



C₂₉ H₄₀ N₂ O₃; Mol wt: 464.6460

ACTION – Neuroprotective agent, a free radical scavenger and lipid peroxidation inhibitor reported to prevent neuronal cell damage in a cerebral ischemia model in rats. Claimed for the treatment of Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis and cerebral trauma, and for preventing ischemia-induced cell damage. A representative compound from a series of phenyl oxazoles, thiazoles, oxazolines, oxadiazoles and benzoxazoles, wherein the following are also specifically claimed:



Compound	R1	A	X	Formula
266708	Me	-CH2-	HCl	C ₂₈ H ₃₈ N ₂ O ₃ .HCl
266709	Pr	-CH2-	HCl	C ₃₀ H ₄₂ N ₂ O ₃ .HCl
266710	Pr	-(CH2)2-		C ₃₁ H ₄₄ N ₂ O ₃

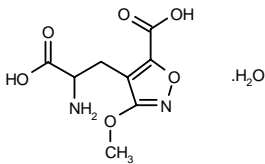
SOURCE – Lilly.

REFERENCES

1. Heinz, L.J. et al. (Eli Lilly and Company) *Novel cpds. useful as neuro-protective agents.* WO 9815274.

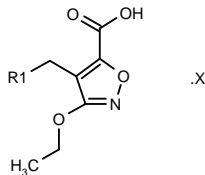
264430

2-Amino-3-(5-carboxy-3-methoxyisoxazol-4-yl)propionic acid hydrate

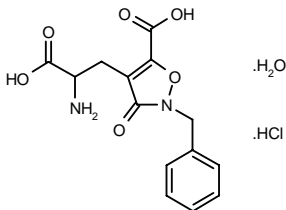


C₈ H₁₀ N₂ O₆ . H₂O; Mol wt: 248.1898

ACTION – Selective AMPA receptor agonist, giving an EC₅₀ value of 1.2 μM in the rat cortical wedge model. Potentially useful for the treatment of cerebral ischemia, Huntington’s disease, epilepsy, Parkinson’s disease, Alzheimer’s disease, schizophrenia, pain, depression and anxiety. Within this series of 3-alkoxyisoxazol-4-yl-substituted 2-amino carboxylic acids, the following are also included:



Compound	R1	X	Formula
267737	(S)-CH(NH ₂)CO ₂ H	H ₂ O	C ₉ H ₁₂ N ₂ O ₅ .H ₂ O
267738	(R)-CH(NH ₂)CO ₂ H	H ₂ O	C ₉ H ₁₂ N ₂ O ₅ .H ₂ O
267740	2-NH ₂ -3,4-dioxo-1-cyclobutenyl-NH		C ₁₁ H ₁₁ N ₃ O ₆



267739: C₁₁ H₁₇ N₂ O₆ . HCl . H₂O

Some compounds within the scope of the invention behave as selective AMPA and/or NMDA antagonists.

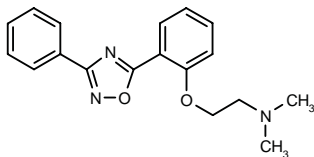
SOURCE – Lundbeck.

REFERENCES

1. Bang-Andersen, B. et al. (Lundbeck A/S) *3-Alkoxyisoxazol-4-yl-substd. 2-amino carboxylic acid cpds.* WO 9815542.

264880

N,N-Dimethyl-*N*-[2-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)-phenoxy]ethyl]amine



C₁₈ H₁₉ N₃ O₂; Mol wt: 309.3671

ACTION – Neuroprotective and cerebral antiischemic agent with high affinity for the sodium channel site 2 binding site and histamine H₁, 5-HT_{1A}, 5-HT_{2A} and σ -receptors (86, 99, 91, 91 and 62% inhibition, respectively, at 10 μ M), as well as AMPA receptor-antagonist activity (86% inhibition of kainate-induced current in neuronal cells at 100 μ M). *In vivo* compound was found to be active in a model of permanent focal cerebral ischemia in rats.

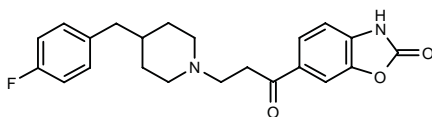
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Brenner, M. et al. (Boehringer Ingelheim GmbH) *Oxadiazoles, processes for their preparation and their use as medicaments*. WO 9817652.

265121

6-[3-(4-Fluorobenzyl)piperidin-1-yl]propionyl]-2,3-dihydro-benzoxazol-2-one



C22 H23 F N2 O3; Mol wt: 382.4327

ACTION – Agent for the treatment of neurodegenerative disorders such as cerebrovascular disorders, epilepsy, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebral ischemia and psychoses with excitatory amino acid-antagonist activity. Compound inhibited [³H]-ifenprodil binding to NMDA receptors in rat cerebral cortex homogenates with an IC₅₀ value of 3.9 \pm 1.6 nM vs. 23.3 \pm 5.1 and 97.0 \pm 12.1 nM, respectively, for ifenprodil and eliprodil; it also inhibited [³H]-MK-801 binding to NMDA receptors in rat cortex homogenates with an IC₅₀ value of 16.7 \pm 2.5 nM vs. 5950 \pm 3985 and 6630 \pm 2800 nM, respectively, for ifenprodil and eliprodil. In addition, it was found to potently inhibit NMDA-stimulated [³H]-GABA release (IC₅₀ = 77.8 \pm 56 nM vs. 690 \pm 173 nM for ifenprodil and 1760 \pm 851 nM for eliprodil).

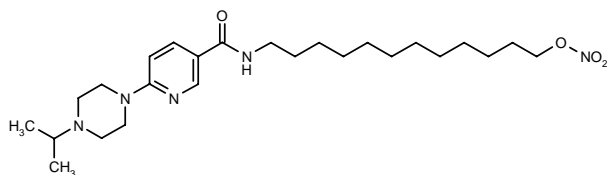
SOURCE – Merck KGaA.

REFERENCES

1. Prücher, H. et al. (Merck Patent GmbH) *Benzoxazole deriv. with an affinity to binding sites of amino acid receptors*. WO 9818793.

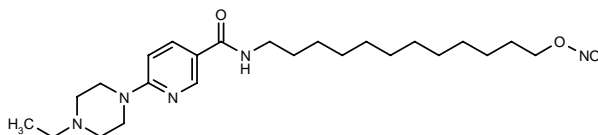
265514

6-(4-Isopropylpiperazin-1-yl)-N-[12-(nitrooxy)dodecyl]-pyridine-3-carboxamide



C25 H43 N5 O4; Mol wt: 477.6457

ACTION – Agent for the treatment of cerebrovascular disorders shown to potently inhibit cerebral edema in a polyvinyl acetate-induced ischemia model in rats (59.1% inhibition at 1 mg/kg i.v.) and in an ischemia–reperfusion model in stroke-prone spontaneously hypertensive rats (71% inhibition at 1 mg/kg i.v.). In addition, compound was found to inhibit delayed neuronal death in rat hippocampal preparations and to inhibit lipid peroxidation in rat brain homogenates (71% inhibition at 100 μ M). Another compound from this series of pyridinecarboxamides is:



266577: C24 H41 N5 O4

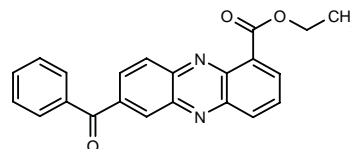
SOURCE – Nisshin Flour Milling.

REFERENCES

1. Oshida, N. et al. (Nisshin Flour Milling Co., Ltd.) *Pyridinecarboxamide derivs*. EP 882716, WO 9822439, WO 9822440.

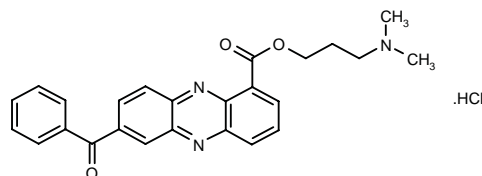
266218

7-Benzoylphenazine-1-carboxylic acid ethyl ester



C22 H16 N2 O3; Mol wt: 356.3794

ACTION – Agent for the treatment of neurodegenerative disorders that acts by inhibiting neuronal cell death. Compound exhibited EC₅₀ values of 2.0 and 8.2 nM, respectively, against glutamic acid- and BSO-induced toxicity in N18-RE-105 cells, and an EC₂₅ value of 68.1 nM against glutamic acid-induced toxicity in rat hippocampal cells. Compound additionally exhibited lipid peroxidation-inhibitory activity (56.6% inhibition at 100 μ M in rat brain homogenates). Another compound from this series of phenazine derivatives is:

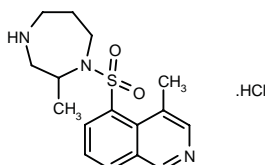


267246: C25 H23 N3 O3 . HCl

SOURCE – Nippon Chemiphar.

REFERENCES

1. Takahashi, T. et al. (Nippon Chemiphar Co., Ltd.) *Phenazine derivs*. JP 98218865, WO 9824773.

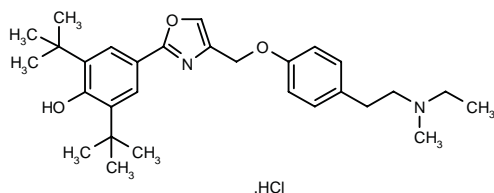
HMN-1152***254945****2-Methyl-1-(4-methylisoquinolin-5-ylsulfonyl)perhydro-1,4-diazepine hydrochloride****(4-Methylisoquinolin-5-yl)(2-methylperhydro-1,4-diazepin-1-yl)sulfone hydrochloride**

C16 H21 N3 O2 S . HCl; Mol wt: 355.8878

ACTION – Vasodilator, a derivative of HA-1077 (fasudil) that appears to act by inhibiting Rho-associated kinase and is more potent as a vasodilator than the latter. Potentially useful for the treatment of delayed vasospasm following subarachnoid hemorrhage.

SOURCE – Nippon Shinyaku.**REFERENCES**

1. Matsuura, A. and Matsuzaki, T. (Nippon Shinyaku Co., Ltd.) *Isoquinoline derivs. and drugs*. WO 9728130.
2. Hidaka, H. *Discovery of novel vascular relaxants by structural biology*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst SG 4.2.
3. Tanaka, H. et al. *Novel vascular relaxant, HMN-1152: Its molecular mechanism of action*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 37.40.

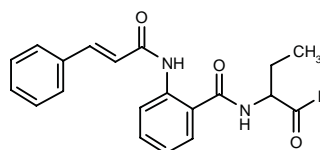
*Identified compound **254945** Drug Data Report 1998, 020(01): 0027.**LY-382924****266976****2,6-Di-*tert*-butyl-4-[4-[4-[2-(*N*-ethyl-*N*-methylamino)-ethyl]phenoxy]methyl]oxazol-2-yl]phenol hydrochloride****2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-4-[4-[2-(*N*-ethyl-*N*-methylamino)ethyl]phenoxy]methyl]oxazole hydrochloride**

C29 H40 N2 O3 . HCl; Mol wt: 501.1069

ACTION – Antioxidant that readily penetrates the blood-brain barrier, with neuroprotective effects in a rat model of global cerebral ischemia. At doses of 2.5 and 5.0 mg/kg/h i.v. for 20 h at the onset of reperfusion (20 min after ischemia), it afforded 35 and 80% protection, respectively, against hippocampal CA1 damage, although no effect was observed at a dose of 1.0 mg/kg/h.

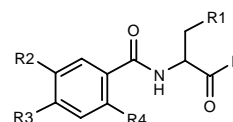
SOURCE – Lilly.**REFERENCES**

1. Heinz, L.J. et al. (Eli Lilly and Company) *Novel cpds. useful as neuro-protective agents*. WO 9815274.
2. Heinz, L.J. et al. *Synthesis and biological evaluation of a novel series of antioxidants for the treatment of global cerebral ischemia*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 130.

MISCELLANEOUS NEUROLOGICAL DRUGS**266172****2-(Cinnamoylamino)-*N*-(1-formylpropyl)benzamide**

C20 H20 N2 O3; Mol wt: 336.3890

ACTION – An inhibitor of cysteine proteases such as calpain and cathepsin B and L, with potential in the treatment of neurodegenerative disorders, cerebral ischemia, stroke, cardiac or renal ischemia, rheumatoid arthritis, muscular dystrophy, restenosis, coronary or cerebral vasospasm, cataracts and cancer. A representative compound from a series of benzamido-aldehydes, wherein the following are also included:



Compound	R1	R2	R3	R4	Isomer	Formula
266788	Ph	2-Naph- -CONH	H	H	S	C ₂₇ H ₂₂ N ₂ O ₃
266789	Ph	H	2-Naph- -CH2O	H	S	C ₂₇ H ₂₃ NO ₃
266790	Ph	H	H	Ph	S	C ₂₂ H ₁₉ NO ₂
266791	Ph	H	(E)-2-Naph- -COCH=CH	H	S	C ₂₉ H ₂₃ NO ₃
266792	Ph	2-Naph- -SO2NH	H	Br	S	C ₂₆ H ₂₁ BrN ₂ O ₄ S
266793	Et	H	8-quinolyl- -SO2NH	H		C ₂₁ H ₂₁ N ₃ O ₄ S
266794	Me	H	H	4-Pyr- -CH=CH		C ₁₈ H ₁₉ ClN ₂ O ₂
266795	Et	H	2-quinolyl- -SCH2	H		C ₂₆ H ₂₆ N ₂ O ₆ S

SOURCE – BASF.**REFERENCES**

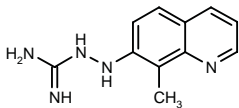
1. Lubisch, W. et al. (BASF AG) *Benzamidoaldehydes and their use as cysteine protease inhibitors*. WO 9823581.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

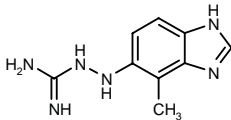
266177

N¹-(8-Methylquinolin-7-ylamino)guanidine



C₁₁ H₁₃ N₅; Mol wt: 215.2587

ACTION – α_2 -Adrenoceptor agonist with potential particularly in the treatment or prevention of nasal congestion. Another specifically claimed compound from this series of guanidinylamino heterocycles is:



267001: C₉ H₁₂ N₆

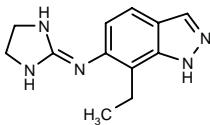
SOURCE – Procter & Gamble.

REFERENCES

1. Cupps, T.L. et al. (The Procter & Gamble Co.) *Guanidinylamino heterocycle cpds. useful as α -2 adrenoceptor agonists.* WO 9823591.

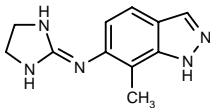
266187

7-Ethyl-6-(imidazolidin-2-ylideneamino)-1*H*-indazole



C₁₂ H₁₅ N₅; Mol wt: 229.2855

ACTION – α_2 -Adrenoceptor agonist with potential particularly in the treatment or prevention of nasal congestion. Another specifically claimed compound from this series of 2-imidazolinylaminoindazole derivatives is:



267002: C₁₁ H₁₃ N₅

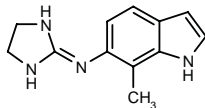
SOURCE – Procter & Gamble.

REFERENCES

1. Cupps, T.L. et al. (The Procter & Gamble Co.) *2-Imidazolinylaminoindazole cpds. useful as α -2 adrenoceptor agonists.* WO 9823609.

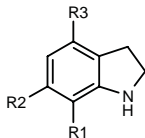
266188

6-(Imidazolidin-2-ylideneamino)-7-methyl-1*H*-indole

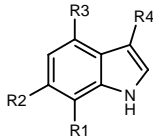


C₁₂ H₁₄ N₄; Mol wt: 214.2706

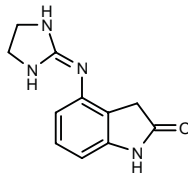
ACTION – α_2 -Adrenoceptor agonist particularly useful in the treatment or prevention of nasal congestion. Other specifically claimed compounds from this series of 2-imidazolinylaminoindoles include the following:



Compound	R1	R2	R3	Formula
267004	Me	imidazolidin-2-yl=N	H	C ₁₂ H ₁₆ N ₄
267006	H	H	imidazolidin-2-yl=N	C ₁₁ H ₁₄ N ₄
267007	Me	H	imidazolidin-2-yl=N	C ₁₂ H ₁₆ N ₄



Compound	R1	R2	R3	R4	Formula
267003	Me	imidazolidin-2-yl=N	H	CN	C ₁₃ H ₁₃ N ₅
267005	H	H	imidazolidin-2-yl=N	Cl	C ₁₁ H ₁₁ ClN ₄



267008: C₁₁ H₁₂ N₄ O

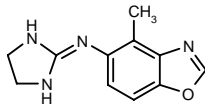
SOURCE – Procter & Gamble.

REFERENCES

1. Henry, R.T. et al. (The Procter & Gamble Co.) *2-Imidazolinylaminoindole cpds. useful as α -2 adrenoceptor agonists.* WO 9823610.

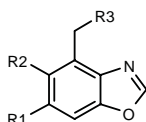
266189

5-(Imidazolidin-2-ylideneamino)-4-methyloxazole



C₁₁ H₁₂ N₄ O; Mol wt: 216.2428

ACTION – α_2 -Adrenoceptor agonist with potential particularly in the treatment or prevention of nasal congestion. A representative compound from a series of 2-imidazolinyaminobenzoxazole derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
267071	H	imidazolidin-2-yl=N	Me	C ₁₂ H ₁₄ N ₄ O
267072	imidazolidin-2-yl=N	H	H	C ₁₁ H ₁₂ N ₄ O
267073	imidazolidin-2-yl=N	H	Me	C ₁₂ H ₁₄ N ₄ O

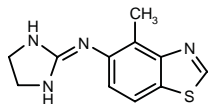
SOURCE – Procter & Gamble.

REFERENCES

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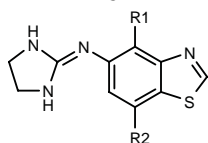
266190

5-(Imidazolidin-2-ylideneamino)-4-methylbenzothiazole

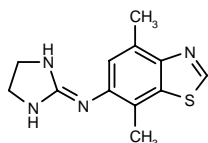


C₁₁ H₁₂ N₄ S; Mol wt: 232.3098

ACTION – α_2 -Adrenoceptor agonist particularly useful for the treatment or prevention of nasal congestion, otitis media and sinusitis. Other specifically claimed compounds from this series of 2-imidazolinyaminobenzothiazoles include the following:



Compound	R1	R2	Formula
267074	OMe	H	C ₁₁ H ₁₂ N ₄ OS
267075	Me	CN	C ₁₂ H ₁₁ N ₅ S
267077	cyclopropyl	H	C ₁₃ H ₁₄ N ₄ S
267078	vinyl	H	C ₁₂ H ₁₂ N ₄ S
267079	Br	H	C ₁₀ H ₉ BrN ₄ S



267076: C₁₂ H₁₄ N₄ S

SOURCE – Procter & Gamble.

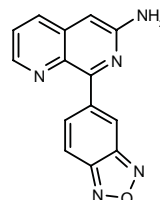
REFERENCES

1. Cupps, T.L. et al. (The Procter & Gamble Co.) 2-Imidazolinyaminobenzothiazole cpds. useful as α_2 adrenoceptor agonists. WO 9823612.

ASTHMA THERAPY

265123

8-(Benzofurazan-5-yl)-1,7-naphthyridin-6-amine



C₁₄ H₉ N₅ O; Mol wt: 263.2591

ACTION – Antiasthmatic and antiinflammatory agent with selective phosphodiesterase type 4 (PDE4)-inhibitory activity. Antiinflammatory activity was demonstrated by its ability to inhibit fMLP-induced activation of human eosinophils (IC₅₀ = 0.006 μ M). It is also reported to downregulate or inhibit tumor necrosis factor (TNF- α) release.

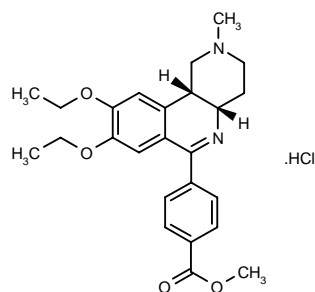
SOURCE – Novartis.

REFERENCES

1. Hersperger, R. (Ciba-Geigy AG) Naphthyridine derivs. WO 9818796.

265492

(–)-cis-4-(8,9-Diethoxy-2-methyl-1,2,3,4,4a,10b-hexahydrobenzo[c][1,6]naphthyridin-6-yl)benzoic acid methyl ester hydrochloride



C₂₅ H₃₀ N₂ O₄ . HCl; Mol wt: 458.9829

ACTION – Bronchodilating and antiinflammatory agent, a selective inhibitor of phosphodiesterase type 4 (PDE4; –logIC₅₀ = 7.54 vs. < 4, 4.80, 6.67 and 5.45 for PDE1, PDE2, PDE3 and PDE5) also reported to possess smooth muscle relaxant properties and cilium frequency-increasing activity. Claimed for use in the treatment of airways disorders and dermatoses.

SOURCE – Byk Gulden.

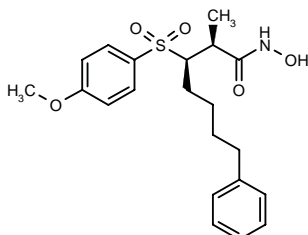
REFERENCES

1. Gutterer, B. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) Benzonaphthyridines as bronchial therapeutics. WO 9821208.

RPR-122818

266872

(2*S*,3*R*)-*N*-Hydroxy-3-(4-methoxyphenylsulfonyl)-2-methyl-7-phenylheptanamide



C21 H27 N O5 S; Mol wt: 405.5123

ACTION – Potent inhibitor of phosphodiesterase type 4 (PDE4; IC_{50} = 32 nM) from a series of arylsulfonyl hydroxamic acids with potential in the treatment of inflammatory disorders.

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

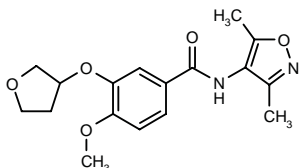
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2. Groneberg, R.D. et al. *The discovery of an arylsulfone hydroxamic acid template for the inhibition of phosphodiesterase type 4 and matrix metalloproteinases.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 001.

RPR-132294

264072

N-(3,5-Dimethylisoxazol-4-yl)-4-methoxy-3-(tetrahydrofuran-3-yloxy)benzamide



C17 H20 N2 O5; Mol wt: 332.3540

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 76.0 ± 1.8 nM in guinea pig macrophages) with selectivity for the low-affinity rolipram binding site. It inhibited lipopolysaccharide-induced tumor necrosis factor (TNF- α) release in dog blood *in vitro* (IC_{50} = 71.6 ± 28.3 nM) and also *ex vivo* following oral administration (43.5% inhibition at 0.03 mg/kg p.o.). Potent inhibition of ovalbumin-induced bronchospasm in anesthetized rats was observed, with an ED_{50} of 0.096 mg/kg p.o., whereas no emesis was seen in dogs at doses of 0.3 mg/kg p.o.

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

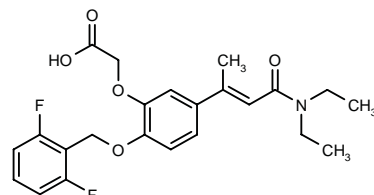
1. Fenton, G. et al. (Rhône-Poulenc Rorer SA) *Subst. aromatic cpds. as cAMP phosphodiesterase- and TNF-inhibitors.* EP 741707, JP 97509654, WO 9520578.

2. Aldous, D. et al. *Biological activity and side effect profile of RPR 132294 and RPR 132703 - Novel PDE₄ inhibitors.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.337.

3. Escott, K.J. et al. *Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs.* Br J Pharmacol 1998, 123(Suppl.): Abst 40P.

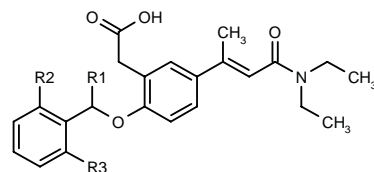
264384

2-[5-[2(*E*)-(N,N-Diethylcarbamoyl)-1-methylvinyl]-2-(2,6-difluorobenzoyloxy)phenoxy]acetic acid



C23 H25 F2 N O5; Mol wt: 433.4485

ACTION – Antiallergic, antiasthmatic and antiinflammatory agent, a selective BLT (LTB₄) receptor antagonist. Compound inhibited [³H]-LTB₄ binding to human neutrophils with an IC_{50} value of 48 nM and the LTB₄-induced increase in intracellular calcium in human neutrophils at a concentration of about 18 nM. *In vivo*, it was active in the arachidonic acid-induced ear edema test in mice, inhibiting edema and myeloperoxidase activity at a dose of 3 mg/kg p.o. at 1.5 h postadministration and at a dose of 10 mg/kg p.o. at 18 h postadministration. Other specifically claimed compounds from this series of aryl-substituted acrylamides include the following:



Compound	R1	R2=R3	Formula
267025	H	F	C ₂₃ H ₂₅ F ₂ NO ₄
267026	Me	H	C ₂₄ H ₂₉ NO ₄

SOURCE – Novartis.

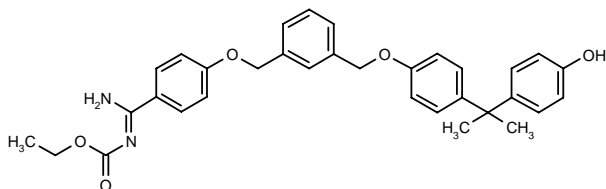
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1. Greenspan, P.D. and Fujimoto, R.A. (Novartis AG) *Aryl-subst. acrylamides with leukotriene B₄ (LTB₄) receptor antagonist activity.* WO 9813347.

BIIL-284^{1,2}

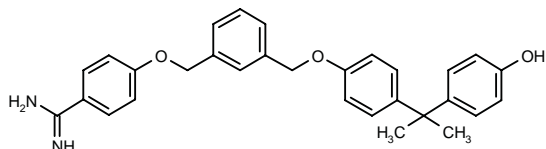
266094

N-(Ethoxycarbonyl)-4-[3-[4-[1-(4-hydroxyphenyl)-1-methylethyl]phenoxy]benzyloxy]benzenecarboximide



C33 H34 N2 O5; Mol wt: 538.6406

ACTION – Specific BLT (LTB_4) receptor antagonist ($K_i = 150$ nM for inhibition of [3H]- LTB_4 binding to human neutrophils), a formate ester prodrug of **BIIL-260** ($K_i = 1.3$ nM) proven to have potent and long-lasting activity *in vivo*: it inhibited LTB_4 -induced mouse ear inflammation with an ED_{50} of 0.008 mg/kg p.o. and LTB_4 -induced neutropenia in monkeys with an ED_{50} of 0.004 mg/kg p.o., the $t_{1/2}$ for the latter effect being 24 h. Currently undergoing phase I trials for the treatment of chronic obstructive pulmonary disease (COPD).



BIIL-260 [266095]²: C₃₀ H₃₀ N₂ O₃

SOURCE – Boehringer Ingelheim.

REFERENCES

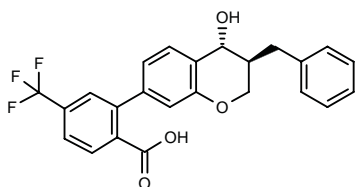
1. Anderskewitz, R. et al. (Boehringer Ingelheim GmbH) *Subst. benzamidines, their production and their use as medicaments*. DE 4424713, EP 770059, JP 98502645, US 5731332, WO 9602497.

2. Norman, P. *COPD: New developments and therapeutic opportunities*. Drug News Perspect 1998, 11(7): 431.

CP-195543

266482

(+)-(3*S*,4*R*)-2-[3-Benzyl-4-hydroxy-3,4-dihydro-2*H*-benzopyran-7-yl]-4-(trifluoromethyl)benzoic acid



C₂₄ H₁₉ F₃ O₄; Mol wt: 428.4041

ACTION – Potent and selective BLT (LTB_4) receptor antagonist, as demonstrated by inhibition of [3H]- LTB_4 binding in human neutrophils and murine spleen membranes ($IC_{50} = 6.8$ and 37.0 nM, respectively; $K_i = 4.9$ and 26.9 nM, respectively), as well as in functional assays by inhibition of LTB_4 -mediated human and murine neutrophil chemotaxis ($IC_{50} = 2.4$ and 7.5 nM, respectively) and by selective blockade of LTB_4 -mediated CD11b upregulation on human ($pA_2 = 7.12$) and mouse neutrophils ($pA_2 = 7.06$) in whole blood. *In vivo*, CP-195543 inhibited LTB_4 -mediated neutrophil infiltration in guinea pig and mouse skin with ED_{50} values of 0.1 and 2.8 mg/kg p.o., respectively, whereas it had no effect against abdominal stretching and prostaglandin production in mice induced by zymosan. The compound was effective in a mouse model of IL-1-exacerbated collagen-induced arthritis when given by osmotic minipump, with half-maximal effects at plasma levels of 0.4-0.5 μ g/ml and complete suppression of clinical disease and weight loss at plasma levels of 2-3 μ g/ml. It is suggested to be suitable for clinical development for a variety of inflammatory disorders.

SOURCE – Pfizer.

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2. Piscopio, A.D. et al. (Pfizer Inc.) *Processes and intermediates for preparing subst. chromanol derivs*. WO 9811085.

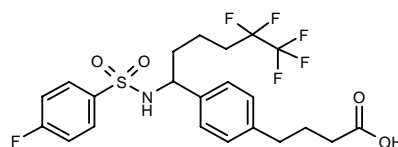
3. Reiter, L.A. et al. *trans-3-Benzyl-4-hydroxy-7-chromanilbenzoic acid derivatives as antagonists of the leukotriene B_4 (LTB_4) receptor*. Bioorg Med Chem Lett 1998, 8(14): 1781.

4. Showell, H.J. et al. *The preclinical pharmacological profile of the potent and selective leukotriene B_4 antagonist CP-195543*. J Pharmacol Exp Ther 1998, 285(3): 946.

RS-601

266248

(\pm)-4-[4-[5,5,6,6,6-Pentafluoro-1-(4-fluorophenyl)sulfonamido]hexyl]phenyl]butanoic acid



C₂₂ H₂₃ F₆ N O₄ S; Mol wt: 511.4807

ACTION – Antiasthmatic agent that acts as a dual TxA_2 and LTD_4 ($CysLT_1$) antagonist, as demonstrated by inhibition of U-46619- and LTD_4 -induced bronchoconstriction in guinea pigs ($ED_{50} = 0.050$ and 0.92 mg/kg p.o., respectively, when given 2 h prior to challenge). It potently suppressed antigen-induced asthma in guinea pigs, almost complete suppression being observed at a dose of 1 mg/kg p.o. given 2 h prior to antigen challenge; its activity was at least comparable if not superior to that of the combination of pranlukast (10 mg/kg) + seratroast (10 mg/kg).

SOURCE – Hokuriku Seiyaku.

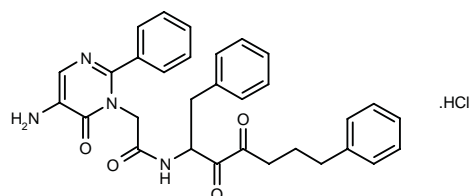
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2. Ohashi, T. et al. *Pharmacological features of RS-601, a novel TxA_2/LTD_4 dual antagonist, in guinea-pig models*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 39.31.

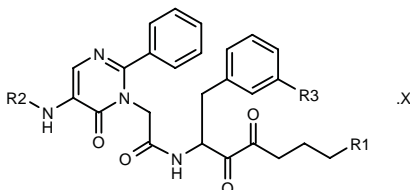
263799

2-(5-Amino-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl)-*N*-(1-benzyl-2,3-dioxo-6-phenylhexyl)acetamide hydrochloride



C₃₁ H₃₀ N₄ O₄ . HCl; Mol wt: 559.0629

ACTION – An inhibitor of chymotrypsin-like proteases with particularly potent activity against chymase (IC_{50} = 46, 13 and 190 nM against rat, dog and human enzyme, respectively) and also active against human elastase (IC_{50} = 1900 nM), but little or no activity against human cathepsin G, human urokinase, human thrombin, human plasmin and human factor Xa (IC_{50} > 10 μ M). The compound inhibited the release of histamine from rat mast cells with an IC_{50} of 1.8 μ M and also inhibited PAF-induced activation of guinea pig peritoneal eosinophils with an IC_{50} of 5.6 μ M. Other compounds from this series of heteroarylacetamide derivatives include the following:



Compound	R1	R2	R3	X	Formula
267342	2-Pyr-O	SO ₂ NHCH ₂ Ph	H	HCl	C ₃₇ H ₃₆ N ₆ O ₇ S.HCl
267343	CO ₂ Et	H	F	HCl	C ₂₈ H ₂₉ FN ₄ O ₆ .HCl
267344	2-Pyr-O	4-Pyr-OCO	H		C ₃₆ H ₃₂ N ₆ O ₇
267345	2-Pyr-O	CHO	H		C ₃₁ H ₂₉ N ₅ O ₆
267346	2-Pyr-O	Ac	H		C ₃₂ H ₃₁ N ₅ O ₆

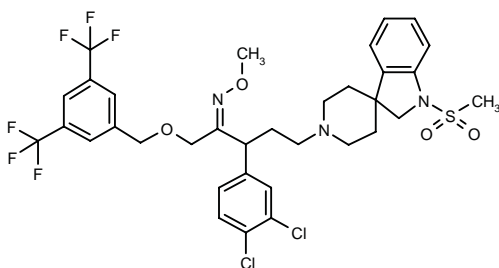
SOURCE – Nippon Kayaku.

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1. Suzuki, Y. and Ishida, K. (Nippon Kayaku Co., Ltd.) *Novel acetamide derivs. and protease inhibitors*. WO 9809949.

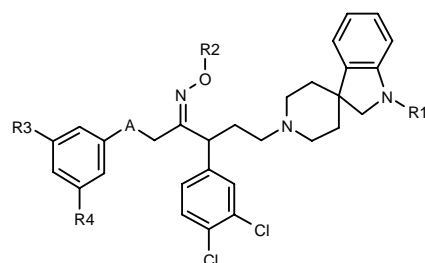
265472

1-[3,5-Bis(trifluoromethyl)benzyloxy]-3-(3,4-dichlorophenyl)-5-[1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-1'-yl]-2-pentanone *O*-methyloxime



C34 H35 Cl₂ F₆ N₃ O₄ S; Mol wt: 766.6275

ACTION – Agent for the treatment of asthma, cough, bronchospasm, inflammatory disorders such as arthritis, CNS disorders such as migraine and epilepsy, gastrointestinal disorders such as Crohn's disease and pain that acts by virtue of its neurokinin receptor-antagonist activity. Other compounds from this series of substituted oximes, hydrazones and olefins include the following:



Compound	R1	R2	R3=R4	A	Formula
266591	CO ₂ CH ₂ Ph	Me	Cl	-CH ₂ O-	C ₃₉ H ₃₉ Cl ₄ N ₃ O ₄
266592	CO ₂ CH ₂ Ph	H	Cl	-CH ₂ O-	C ₃₈ H ₃₇ Cl ₄ N ₃ O ₄
266593	SO ₂ Me	Me	Me	-CON(Me)-	C ₃₅ H ₄₂ Cl ₂ N ₄ O ₄ S
266594	SO ₂ Me	Me	Cl	-CON(Me)-	C ₃₃ H ₃₆ Cl ₄ N ₄ O ₄ S

Some compounds within the scope of the invention show strong NK₁ receptor-antagonist activity and weaker NK₂ and NK₃ receptor-antagonist effects, while others are strong NK₂ antagonists and weaker NK₁ and NK₃ antagonists. Preferred compounds are those with approximately equal potency for the receptor subtypes.

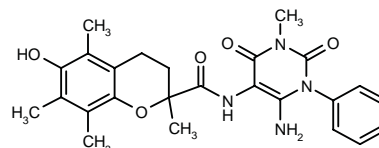
SOURCE – Schering-Plough.

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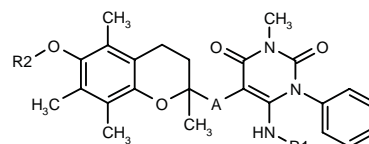
265900

N-(6-Amino-3-methyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C₂₅ H₂₈ N₄ O₅; Mol wt: 464.5192

ACTION – Antiallergic and antiinflammatory agent proven active in a murine model of dermatitis induced by picryl chloride when administered topically at a concentration of 0.25% w/v (69% inhibition). A representative compound from a series of hydroquinone derivatives, wherein the following are also included:



Compound	R1	R2	A	Formula
266921	H	H	-CONH-	C ₂₅ H ₂₈ N ₄ O ₅
266922	H	H	-CONH-	C ₂₅ H ₂₈ N ₄ O ₅
266923	Me	H	-CONH-	C ₂₆ H ₃₀ N ₄ O ₅
266924	H	Me	-CONH-	C ₂₆ H ₃₀ N ₄ O ₅
266925	H	Ac	-CONH-	C ₂₇ H ₃₀ N ₄ O ₆
266927	H	H	-CH ₂ NH-	C ₂₅ H ₃₀ N ₄ O ₄
266928	H	H	-CON(Bu)CH ₂ -	C ₃₀ H ₃₈ N ₄ O ₅

SOURCE – Japan Energy.

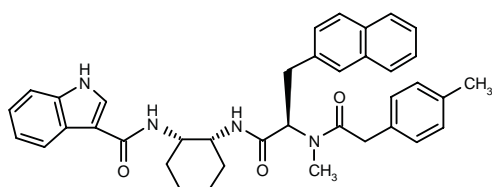
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1. Isobe, Y. et al. (Japan Energy Corp.) *Hydroquinone derivs. and their medicinal use*. JP 98147575, US 5821247.

MEN-11467

266247

N-[2-(4-Methylphenyl)acetyl]-*N*-methyl-(3-naphthyl)-L-alanine *N*-[2-(1*H*-indol-3-ylcarboxamido)cyclohexyl]-amide



C38 H40 N4 O3; Mol wt: 600.7590

ACTION – Pseudopeptide tachykinin NK₁ receptor antagonist ($pK_i = 9.4 \pm 0.1$ and 8.8 ± 0.1 , respectively, for inhibition of [³H]-substance P binding in human lymphoblastoma IM9 and astrocytoma U373 MG cells), with about 1000 times lower affinity for NK₂ ($pK_i = 5.9$ in guinea pig urinary bladder) and NK₃ receptors ($pK_i = 5$ or less in guinea pig cerebral cortex); it shifted the substance P methyl ester-induced concentration–response curve in isolated guinea pig ileum to the right in a nonparallel manner, with progressive inhibition of the maximal response ($pK_b = 10.7 \pm 0.1$), and its effect was slowly reversible. *In vivo*, it was shown to inhibit [Sar⁹,Met(O₂)¹¹]-substance P-induced bronchoconstriction in anesthetized guinea pigs with an ED₅₀ of 29 ± 5 µg/kg i.v. and 670 ± 270 µg/kg i.d., with a duration of action of over 3 h; it also dose-dependently inhibited plasma protein extravasation induced by this agonist in guinea pig bronchi (ED₅₀ = 6.7 ± 2.2 mg/kg p.o.) and markedly reduced antigen-induced plasma protein extravasation in the bronchi of sensitized guinea pigs at doses of 1 and 3 mg/kg p.o.

SOURCE – Menarini.

REFERENCES

1. Cirillo, R. et al. *Pharmacology of MEN 11467, a potent, selective and orally effective pseudopeptide tachykinin NK-1 antagonist*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 39.10.

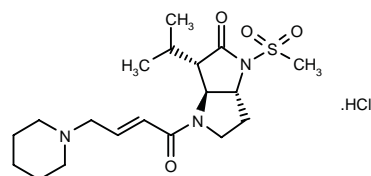
TREATMENT OF RDS AND EMPHYSEMA

GW-311616A*

251429

257181 (as free base)

(3*S*,3*aS*,6*aR*)-3-Isopropyl-1-(methanesulfonyl)-4-[4-(1-piperidinyl)-2(*E*)-butenoyl]perhydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one hydrochloride



C19 H31 N3 O4 S . HCl; Mol wt: 433.9978

ACTION – A potent and selective inhibitor of human neutrophil elastase (HNE; IC₅₀ = 22 nM) with little or no activity against trypsin or chymotrypsin (IC₅₀ > 1000 nM), derived from the natural polycyclic fused *trans*-lactone GW-133686X. Potentially useful in the treatment of respiratory disorders such as chronic bronchitis.

SOURCE – Glaxo Wellcome.

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1. Dowle, M.D. et al. (Glaxo Wellcome plc) *Pyrrolopyrrolone derivs. as inhibitors of neutrophil elastase*. WO 9736903.

2. Johnson, M.R. et al. *The discovery and synthesis of some bicyclic trans-lactams having potent neutrophil elastase inhibitory properties*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.215.

3. Macdonald, S.J.F. et al. *The medicinal chemistry of trans-5-oxo-hexahydropyrrolo-(3,2-b)pyrroles as elastase inhibitors leading to the development candidate GW311616*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 006.

4. *Glaxo Wellcome Compounds in Development*. Glaxo Wellcome plc Company Communication 1997, May 2.

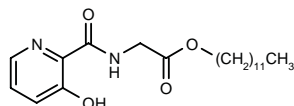
5. *Glaxo Wellcome's R&D pipeline remains full and diverse*. Prous Science Daily Essentials 1998, Jan 21.

*Identified compound **257181** Drug Data Report 1998, 020(01): 0036.

TREATMENT OF CYSTIC FIBROSIS

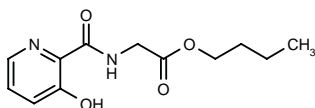
265427

N-(3-Hydroxypyridin-2-ylcarbonyl)glycine dodecyl ester



C20 H32 N2 O4; Mol wt: 364.4828

ACTION – Agent for the treatment of fibrotic disorders such as in the lungs, skin and eye, as well as glaucoma and atherosclerosis, that acts by inhibiting collagen biosynthesis through inhibition of prolyl-4-hydroxylase (proline hydroxylase), as shown in normal human skin fibroblasts (50% inhibition at 0.6 μ M) and rat liver epithelial cells (100% inhibition at 25 μ M). Another compound from this series of 3-hydroxypyridin-2-carboxamides is:



266635: C12 H16 N2 O4

SOURCE – Hoechst Marion Roussel.

REFERENCES

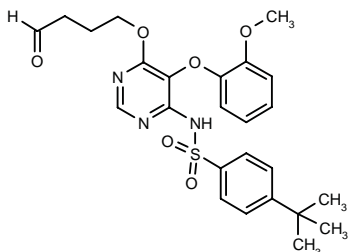
1. Weidmann, K. et al. (Hoechst AG) *3-Hydroxypyridine-2-carboxylic acid amide esters, their preparation and their use as medicaments*. EP 846685, JP 98168062.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

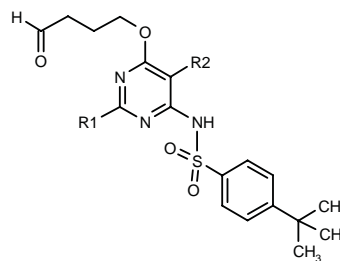
261536

4-*tert*-Butyl-*N*-[6-(3-formylpropoxy)-5-(2-methoxyphenoxy)pyrimidin-4-yl]benzenesulfonamide



C25 H29 N3 O6 S; Mol wt: 499.5851

ACTION – Endothelin receptor antagonist with high selectivity for ET_B receptors over ET_A receptors (IC₅₀ = 0.15 vs. 910 nM; ET_A/ET_B ratio = 6067) and potential in the treatment of hypertension, renal failure, heart failure, renal ischemia, cerebral ischemia, cerebral infarction, cerebral edema and migraine. Within this series of pyrimidine derivatives, the following are also included:



Compound	R1	R2	Formula
266446	H	3-MeO-PhO	C ₂₅ H ₂₉ N ₃ O ₆ S
266447	H	1,4-benzodioxan-5-yl-O	C ₂₆ H ₂₉ N ₃ O ₇ S
266448	Ph	3-MeO-PhO	C ₃₁ H ₃₃ N ₃ O ₆ S
266449	Ph	4-Me-Ph	C ₃₁ H ₃₃ N ₃ O ₄ S
266450	H	2-Me-5-MeO-PhO	C ₂₆ H ₃₁ N ₃ O ₆ S
266451	H	3-OH-PhO	C ₂₄ H ₂₇ N ₃ O ₆ S
266452	H	2-OH-PhO	C ₂₄ H ₂₇ N ₃ O ₆ S

SOURCE – Shionogi.

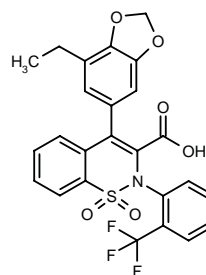
REFERENCES

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PD-180988

266870

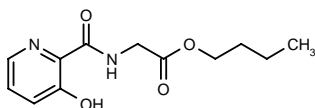
4-(7-Ethyl-1,3-benzodioxol-5-yl)-2-[2-(trifluoromethyl)phenyl]-2*H*-1,2-benzothiazine-3-carboxylic acid *S,S*-dioxide



C25 H18 F3 N O6 S; Mol wt: 517.4782

ACTION – Potent and selective endothelin ET_A receptor antagonist, as demonstrated in binding studies (IC₅₀ = 0.46 nM for cloned human ET_A receptors vs. IC₅₀ = 2200 nM for cloned human ET_B receptors) and in functional studies by inhibition of ET_A-mediated ET-1-induced vasoconstriction in rabbit femoral artery (K_b = 0.026 nM). PD-180988 was rapidly absorbed in rats and showed high oral bioavailability (60-75%).

ACTION – Agent for the treatment of fibrotic disorders such as in the lungs, skin and eye, as well as glaucoma and atherosclerosis, that acts by inhibiting collagen biosynthesis through inhibition of prolyl-4-hydroxylase (proline hydroxylase), as shown in normal human skin fibroblasts (50% inhibition at 0.6 μ M) and rat liver epithelial cells (100% inhibition at 25 μ M). Another compound from this series of 3-hydroxypyridin-2-carboxamides is:



266635: C12 H16 N2 O4

SOURCE – Hoechst Marion Roussel.

REFERENCES

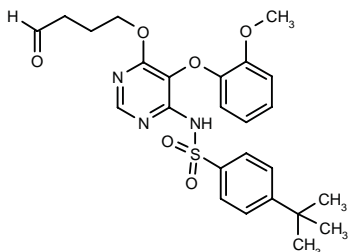
1. Weidmann, K. et al. (Hoechst AG) *3-Hydroxypyridine-2-carboxylic acid amide esters, their preparation and their use as medicaments*. EP 846685, JP 98168062.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

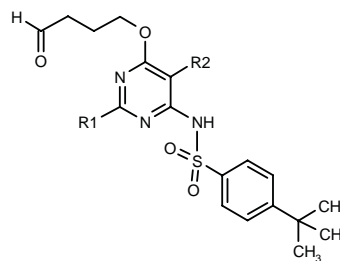
261536

4-*tert*-Butyl-*N*-[6-(3-formylpropoxy)-5-(2-methoxyphenoxy)pyrimidin-4-yl]benzenesulfonamide



C25 H29 N3 O6 S; Mol wt: 499.5851

ACTION – Endothelin receptor antagonist with high selectivity for ET_B receptors over ET_A receptors (IC₅₀ = 0.15 vs. 910 nM; ET_A/ET_B ratio = 6067) and potential in the treatment of hypertension, renal failure, heart failure, renal ischemia, cerebral ischemia, cerebral infarction, cerebral edema and migraine. Within this series of pyrimidine derivatives, the following are also included:



Compound	R1	R2	Formula
266446	H	3-MeO-PhO	C ₂₅ H ₂₉ N ₃ O ₆ S
266447	H	1,4-benzodioxan-5-yl-O	C ₂₆ H ₂₉ N ₃ O ₇ S
266448	Ph	3-MeO-PhO	C ₃₁ H ₃₃ N ₃ O ₆ S
266449	Ph	4-Me-Ph	C ₃₁ H ₃₃ N ₃ O ₄ S
266450	H	2-Me-5-MeO-PhO	C ₂₆ H ₃₁ N ₃ O ₆ S
266451	H	3-OH-PhO	C ₂₄ H ₂₇ N ₃ O ₆ S
266452	H	2-OH-PhO	C ₂₄ H ₂₇ N ₃ O ₆ S

SOURCE – Shionogi.

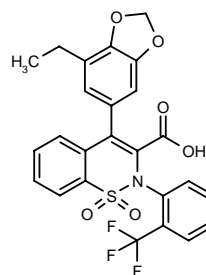
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PD-180988

266870

4-(7-Ethyl-1,3-benzodioxol-5-yl)-2-[2-(trifluoromethyl)phenyl]-2*H*-1,2-benzothiazine-3-carboxylic acid *S,S*-dioxide



C25 H18 F3 N O6 S; Mol wt: 517.4782

ACTION – Potent and selective endothelin ET_A receptor antagonist, as demonstrated in binding studies (IC₅₀ = 0.46 nM for cloned human ET_A receptors vs. IC₅₀ = 2200 nM for cloned human ET_B receptors) and in functional studies by inhibition of ET_A-mediated ET-1-induced vasoconstriction in rabbit femoral artery (K_b = 0.026 nM). PD-180988 was rapidly absorbed in rats and showed high oral bioavailability (60-75%).

SOURCE – Warner-Lambert.

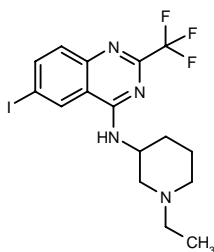
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PD-159790*

240837

N-(1-Ethylpiperidin-3-yl)-*N*-[6-iodo-2-(trifluoromethyl)quinazolin-4-yl]amine



C₁₆H₁₈F₃I N₄; Mol wt: 450.2402

ACTION – Selective endothelin-converting enzyme (ECE) inhibitor proven to inhibit the conversion of big ET-1 in human umbilical vein endothelial cells (HUVEC) at picomolar concentrations. Claimed in patent literature for the treatment of a wide range of disorders including hypertension, congestive heart failure, myocardial infarction, subarachnoid hemorrhage, cerebral ischemia or infarction, diabetes, restenosis, acute and chronic renal failure and cancer.

SOURCE – Warner-Lambert.

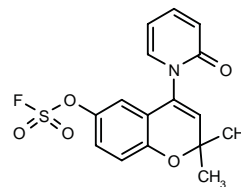
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2. Russell, F.D. et al. *Evidence for an intracellular endothelin converting enzyme in human endothelial cells*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 16.14.

*Identified compound **240837** (see **239034**) Drug Data Report 1996, 018(10): 0882.

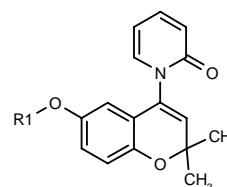
264721

1-[6-(Fluorosulfonyloxy)-2,2-dimethyl-2H-[1]benzopyran-4-yl]-2-pyridinone



C₁₆H₁₄F N O₅ S; Mol wt: 351.3526

ACTION – Potassium channel activator with a pEC₅₀ value of 7.95 in rat aortic rings precontracted with K⁺ and of 7.22 in rat tracheal strips precontracted with carbachol, and respective E_{max} values of 70 and 90%. Other compounds from this series of 6-oxy derivatives of benzopyrans include the following:



Compound	R1	Formula
EMD-67618 [264505]	H	C ₁₆ H ₁₅ NO ₃
EMD-67617 [264722]	Me	C ₁₇ H ₁₇ NO ₃

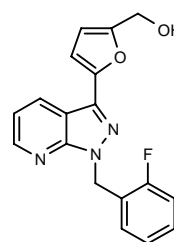
SOURCE – Merck KGaA.

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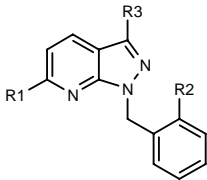
266197

1-(2-Fluorobenzyl)-3-[5-(hydroxymethyl)furan-2-yl]-1*H*-pyrazolo[3,4-*b*]pyridine



C₁₈H₁₄F N₃ O₂; Mol wt: 323.3256

ACTION – Vasorelaxant and platelet aggregation inhibitor for the treatment of cardiovascular disorders such as hypertension, heart failure, angina pectoris and arrhythmias, thromboembolic disorders such as myocardial infarction and ischemia, restenosis following thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis and urogenital system disorders such as prostate hypertrophy, erectile dysfunction and urinary incontinence. *In vitro*, compound was found to potently stimulate guanylate cyclase in primary endothelial cells (> 1000% increase in cGMP levels at 1 µM) and to inhibit phenylephrine-induced contractions of guinea pig aorta strips (IC₅₀ = 1.8 µM). *In vivo*, it produced a maximum decrease in blood pressure of 18 mmHg when given to anesthetized rats at 10 mg/kg p.o. Other compounds from this series of substituted pyrazole derivatives include the following:



Compound	R1	R2	R3	Formula
267083	H	H	5-(CH ₂ OH)-2-furyl	C ₁₈ H ₁₅ N ₃ O ₂
267084	H	F	2-furyl	C ₁₇ H ₁₂ FN ₃ O
267085	H	F	2-pyrimidinyl	C ₁₇ H ₁₂ FN ₅
267086	H	F	2-Pyr	C ₁₈ H ₁₃ FN ₄
267087	OH	F	5-CHO-2-furyl	C ₁₈ H ₁₂ FN ₃ O ₃

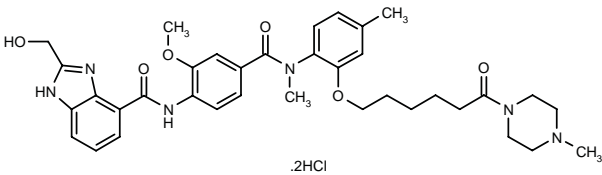
SOURCE – Bayer.

REFERENCES

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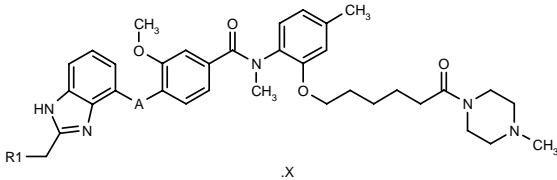
267414

4-[2-(Hydroxymethyl)-1*H*-benzimidazol-4-ylcarboxamido]-3-methoxy-*N*-methyl-*N*-[4-methyl-2-[5-(4-methylpiperazin-1-ylcarbonyl)pentyl]oxy]phenyl]benzamide dihydrochloride



C36 H44 N6 O6 . 2HCl; Mol wt: 729.7014

ACTION – Vasopressin antagonist with selectivity for V₁ receptors (IC₅₀ < 1.0 nM) relative to V₂ receptors (IC₅₀ = 380 nM), potentially useful in the treatment or prevention of hypertension, heart failure, renal insufficiency, edema, ascites, hepatocirrhosis, hyponatremia, hypokalemia, circulation disorders, cerebrovascular disorders, Meniere's syndrome or motion sickness. Within this series of benzamide derivatives, the following are also included:



Compound	R1	A	X	Formula
267415	NH ₂	-CONH-	3HCl	C ₃₆ H ₄₅ N ₇ O ₅ ·3HCl
267416	H	-NHCO-	2HCl	C ₃₆ H ₄₄ N ₆ O ₅ ·2HCl
267417	4-Me-1-Piz	-NHCO-	3HCl	C ₄₁ H ₅₄ N ₈ O ₅ ·3HCl

SOURCE – Fujisawa.

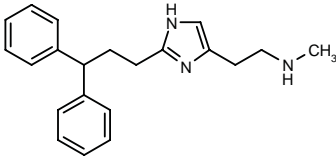
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METHYLHISTAPRODIFEN

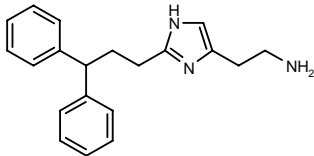
266339

2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]-*N*-methyl-1-ethanamine



C21 H25 N3; Mol wt: 319.4495

ACTION – Highly potent and selective histamine H₁ receptor agonist proven to be more potent than histamine as regards contractile effects in guinea pig ileum (relative activity [histamine = 100%] = 343%) and aorta (relative activity = 458%). It produced a dose-dependent reduction in blood pressure in pithed rats with a pED₅₀ value of 8.43, an effect that was antagonized by the H₁ antagonist dimethindene, but not by the H₂ antagonist ranitidine, the H₃ antagonist thioperamide or adrenalectomy; no effect was observed on heart rate. Another member of this new class of so-called histaprodifens is:



Histaprodifen [266340]: C20 H23 N3

SOURCE – Freie Universität Berlin, Berlin (DE).

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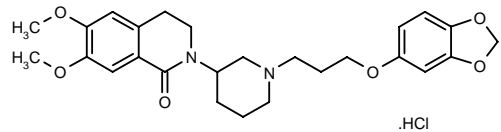
3. Kramer, K. et al. *Histaprofiden and Nalpha-substituted derivatives: A new class of selective and highly potent histamine H1-receptor agonists.* Eur J Pharm Sci 1998, 6(Suppl. 1): Abst 22.

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TREATMENT OF DISORDERS OF
THE CORONARY ARTERIES

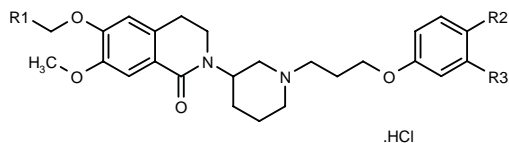
264389

2-[1-[3-(1,3-Benzodioxol-5-yloxy)propyl]piperidin-3-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-one hydrochloride



C26 H32 N2 O6 . HCl; Mol wt: 505.0077

ACTION – Bradycardic agent that inhibits I_f currents, shown to reduce heart rate in guinea pig right atrium preparations with an EC₃₀ value of 0.07 μM. Potentially useful in the treatment or prevention of angina pectoris, myocardial infarction, congestive heart failure and irregular pulse. A representative compound from a series of 1,2,3,4-tetrahydroisoquinoline derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
267337	Me	-OCH2O-		C ₂₇ H ₃₄ N ₂ O ₆ .HCl
267338	H	OMe	H	C ₂₆ H ₃₄ N ₂ O ₅ .HCl
267339	H	CO2Me	H	C ₂₇ H ₃₄ N ₂ O ₆ .HCl
267340	H	OEt	H	C ₂₇ H ₃₆ N ₂ O ₅ .HCl
267341	Me	OMe	OMe	C ₂₈ H ₃₈ N ₂ O ₆ .HCl

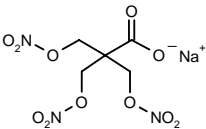
SOURCE – Yamanouchi.

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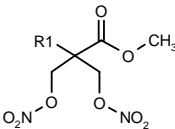
264425

3-(Nitrooxy)-2,2-bis(nitrooxymethyl)propionic acid sodium salt



C5 H6 N3 Na O11; Mol wt: 307.1024

ACTION – Vasodilator, a representative compound from a series of pentaerythritol derivatives reported to possess improved nitric oxide (NO)-donor properties compared to glyceryl trinitrate and isosorbide 5-mononitrate. Other specifically claimed compounds include the following:



Compound	R1	Formula
267821	CH2ONO2	C ₆ H ₉ N ₃ O ₁₁
267822	CO2Me	C ₇ H ₁₀ N ₂ O ₁₀

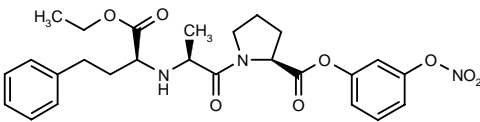
SOURCE – Isis Pharmaceuticals.

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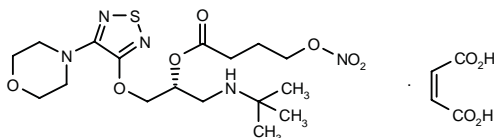
265486

N-1(S)-(Ethoxycarbonyl)-3-phenylpropyl-L-alanyl-L-proline 3-(nitrooxy)phenyl ester



C26 H31 N3 O8; Mol wt: 513.5439

ACTION – Nitrate ester of enalapril which possesses potent antithrombotic activity in addition to the antihypertensive activity of enalapril and an improved safety profile, thus exhibiting a greatly improved profile compared to parent compound for the treatment of cardiovascular disorders such as myocardial or cerebral infarction and atherosclerosis. Compound produced 65% inhibition of platelet aggregation induced by collagen in rats at 10 mg/kg p.o. vs. 15% inhibition for enalapril at the same dose; at this dose, compound also produced 53% inhibition of collagen-induced thrombosis in rats compared to 11% inhibition for enalapril. Contrary to enalapril, it was able to inhibit L-NAME-induced hypertension in rats at 10 mg/kg i.v. In addition, it produced a more pronounced and longer lasting reduction in intraocular pressure than enalapril in rabbits following topical application of 100 µg. Compound exhibited a reduced liability to cause cough typically associated with angiotensin-converting enzyme (ACE) inhibitors, as shown by its ability to reduce capsaicin-induced bronchoconstriction in rats, contrary to enalapril, which markedly enhanced the bronchoconstrictive response. Another compound from this series of nitrate derivatives of known cardiovascular drugs is:



266604: C₁₇ H₂₉ N₅ O₇ S . C₄ H₄ O₄

SOURCE – NicOx.

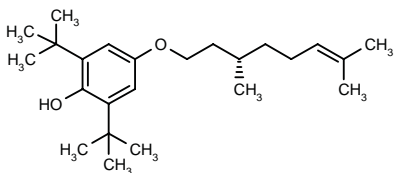
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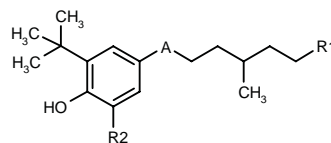
265507

2,6-Di-*tert*-butyl-4-[3(*S*),7-dimethyl-6-octenyloxy]phenol



C₂₄ H₄₀ O₂; Mol wt: 360.5780

ACTION – Agent for the treatment of atherosclerosis and chronic inflammatory disorders such as asthma, rheumatoid arthritis, autoimmune diabetes, transplant rejection and tumor angiogenesis with VCAM-1 and ICAM-1 expression-inhibitory activity, LDL peroxidation-inhibitory activity, cholesterol-lowering activity and antioxidant properties, as shown in several experimental assays. Other compounds from this series of substituted phenols and thiophenols include the following:



Compound	R1	R2	A	Isomer	Formula
MDL-103649 [266779]	CH=C(Me) ₂	H	O	S	C ₂₀ H ₃₂ O ₂
MDL-103714 [266780]	CH=C(Me) ₂	H	S	S	C ₂₀ H ₃₂ OS
MDL-103960 [266781]	CH=C(Me) ₂	t-Bu	S		C ₂₄ H ₄₀ OS
MDL-104102 [266782]	i-Bu	t-Bu	O		C ₂₄ H ₄₂ O ₂
MDL-104191 [266783]	i-Bu	H	O		C ₂₀ H ₃₄ O ₂
MDL-104487 [266784]	CH ₂ C(Me) ₂ OH	t-Bu	S		C ₂₄ H ₄₂ O ₂ S
MDL-104535 [266785]	CH=C(Me) ₂	t-Bu	O	R	C ₂₄ H ₄₀ O ₂
MDL-105411 [266786]	CH=C(Me) ₂	H	O		C ₂₀ H ₃₂ O ₂
MDL-107059 [266787]	CH=C(Me) ₂	H	O	S	C ₂₄ H ₄₀ O ₂

SOURCE – Hoechst Marion Roussel.

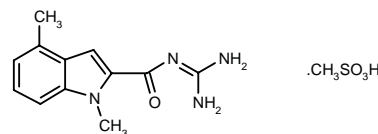
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SM-20550

248768

N'-(1,4-Dimethyl-1*H*-indol-2-ylcarbonyl)guanidine mesylate



C₁₂ H₁₄ N₄ O . C₄ H₄ O₃ S; Mol wt: 326.3752

ACTION – Cardioprotective agent, a potent and selective Na⁺/H⁺ exchange inhibitor proven to significantly improve cardiac function and coronary circulation and prevent creatine phosphokinase release and increase in tissue Ca²⁺ contents at concentrations of 10-100 nM in isolated perfused rat hearts subjected to ischemia/reperfusion. In anesthetized rats, it produced a dose-dependent (0.03-0.3 mg/kg i.v.) reduction in arrhythmias induced by reperfusion following coronary artery occlusion. SM-20550 at a dose of 0.17 mg/kg i.v. before ischemia followed by 0.28 mg/kg/h significantly improved coronary vasodilator reserve and reduced myocardial infarct size (11 ± 2% vs. 54 ± 5% in controls) in dogs subjected to 2 h of left circumflex coronary artery occlusion followed by 5 h of reperfusion; it was less active when given starting just before reperfusion (32 ± 4% reduction in infarct size). Similar results were obtained in anesthetized open-chest rabbits. It appears to be devoid of cardiodepressive or hypotensive effects.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

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2. Kojima, A. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Indoloylguanidine derivs. as inhibitors of sodium-hydrogen exchange.* CA 2121391, EP 622356, JP 95010839.

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7. Matsui, K. et al. *Cardioprotective effect of a new Na⁺/H⁺ exchange inhibitor, SM-20550, on ischemic reperfusion injury.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst P-458.

8. Matsui, K. et al. *Cardioprotective effect of SM-20550, a new Na⁺/H⁺ exchange inhibitor, on ischemic reperfusion-induced myocardial infarction and stunning in rabbits and dogs.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 36.78.

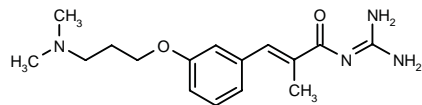
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ANTIARRHYTHMIC DRUGS

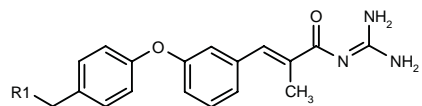
265931

N²-[3-[3-[3-(Dimethylamino)propoxy]phenyl]-2-methyl-2(E)-propenoyl]guanidine



C16 H24 N4 O2; Mol wt: 304.3916

ACTION – Antiischemic and antiarrhythmic agent with excellent Na⁺/H⁺ exchange-inhibitory activity. A representative compound from a series of 3-arylacryloylguanidine derivatives, wherein the following are also included:



Compound	R1	Formula
268288	N(Me)2	C ₂₀ H ₂₄ N ₄ O ₂
268289	OH	C ₁₈ H ₁₈ N ₃ O ₃

SOURCES – Merck KGaA; Yamanouchi.

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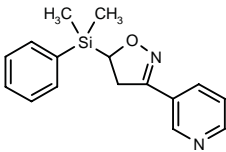
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HEART FAILURE THERAPY

IOS-7578

266337

3-[5-[Dimethyl(phenyl)silyl]-4,5-dihydro-3-isoxazolyl]-pyridine



C16 H18 N2 O Si; Mol wt: 282.4172

ACTION – Vasodilator and antithrombotic agent that demonstrated cardioprotective effects in an experimental model of ischemia/reperfusion-induced heart failure in rats, protecting against the depression in myocardial function during occlusion and at the end of reperfusion and reducing lethality at a dose of 2 mg/kg i.v.

SOURCE – Latvian Institute of Organic Synthesis, Riga (LV).

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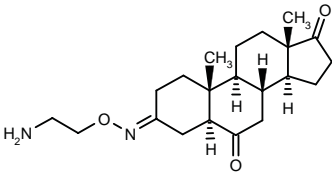
2. Veveris, M. et al. *Nitric oxide effect on ischaemia-reperfusion induced heart failure: Pharmacological modulation.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 18.15.

PST-2744

266338

3-(2-Aminoethoxyimino)-5 α -androstane-6,17-dione

5- α -Androstane-3,6,17-trione 3-[O-(2-aminoethyl)oxime]



C21 H32 N2 O3; Mol wt: 360.4948

ACTION – Inotropic agent, a potent Na⁺/K⁺-ATPase inhibitor structurally unrelated to cardiac glycosides (digitalis) proven to displace [³H]-ouabain binding from dog kidney Na⁺/K⁺-ATPase α1 isoform with a K_i of 250 nM (K_i digoxin = 500 nM) and to inhibit enzyme activity with a K_i of 50 nM (K_i digoxin = 60 nM). In isolated, electrically paced guinea pig left atria, it increased the force of contraction (EC₅₀ = 3.5 ± 0.29 μM; 140%) with efficacy and potency similar to digoxin (EC₅₀ = 0.48 ± 0.04 μM; 180%), and the concentration inducing arrhythmias was 30-fold the EC₅₀ compared to only 6-fold for digoxin. In anesthetized guinea pigs, PST-2744 (0.16 ml/min of 0.05% solution) increased +dP/dt by 139 ± 14% without affecting heart rate or blood pressure; at doses slightly greater than the maximum inotropic dose, digoxin was associated with a mortality rate of 66%, whereas no deaths were observed in animals treated under similar conditions with PST-2744.

SOURCE – Sigma-Tau.

REFERENCES

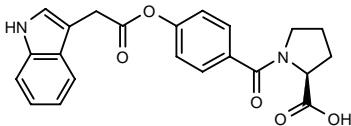
1. De Munari, S. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *New 6-hydroxy and 6-oxo-androstane derivs. active on the cardiovascular system and pharmaceutical compns. containing the same*. EP 825197, JP 98077292.

2. Micheletti, R. and Schiavone, A. *PST 2744, a potent Na,K-ATPase inhibitor structurally unrelated to cardiac glycosides*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.26.

MISCELLANEOUS
CARDIOVASCULAR DRUGS

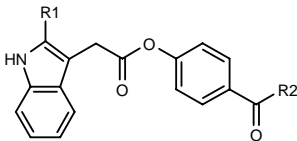
264327

1-[4-[2-(1*H*-Indol-3-yl)acetoxy]benzoyl]-L-proline



C22 H20 N2 O5; Mol wt: 392.4090

ACTION – Agent for the treatment or prevention of circulatory disorders, an inhibitor of human chymase (IC₅₀ = 0.015 μM). A representative compound from a series of phenol ester derivatives, wherein the following are also included:



Compound	R1	R2	Formula
267422	H	4-CO2H-1-Pip	C ₂₃ H ₂₂ N ₂ O ₅
267423	H	3(S)-CO2H-1,2,3,4-tetrahydro-2-isoquinolyl	C ₂₇ H ₂₂ N ₂ O ₅
267424	Me	-L-Pro-OH	C ₂₃ H ₂₂ N ₂ O ₅

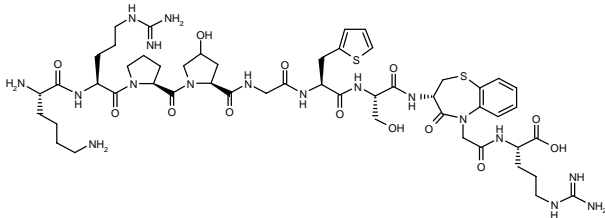
SOURCE – Takeda.

REFERENCES

1. Tamura, N. et al. (Takeda Chemical Industries, Ltd.) *Phenol ester derivs., their preparation method and their use*. JP 98087567.

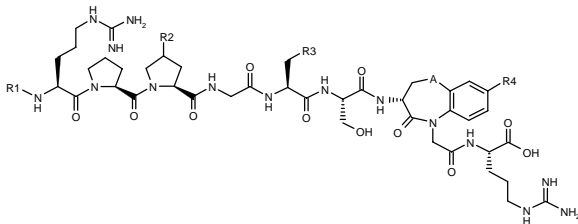
266233

N-[2-[3(S)-[L-Lysyl-L-arginyl-L-prolyl-L-(4-hydroxy)prolyl-glycyl-L-(2-thienyl)alanyl-L-serylamino]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl]acetyl]-L-arginine



C51 H77 N17 O13 S2; Mol wt: 1200.4070

ACTION – Bradykinin B₂ receptor agonist, as demonstrated in a binding assay by a K_i value of 0.07 nM using human B₂ receptors cloned in CHO cells (K_i = 0.5 nM for bradykinin), as well as in a functional assay in human umbilical vein, where it exhibited a pD₂ value of 7.1 vs. 7.3 for bradykinin. Potentially useful for the treatment of cardiovascular disorders, particularly myocardial ischemia, as well as for enhancing the permeability of the blood–brain barrier and for improving genital function (inducing ovulation, improving sperm motility and inducing uterine contractions). Within this series of pseudo-peptides, the following are also included:



Compound	R1	R2	R3	R4	A	Formula
267531	H-D-Arg-	OH	2-thienyl	H	S	C ₅₁ H ₇₇ N ₁₉ O ₁₃ S ₂
267532	H	H	Ph	H	S	C ₄₇ H ₆₇ N ₁₅ O ₁₁ S
267533	H-D-Arg-	OH	2-thienyl	H	O	C ₅₁ H ₇₇ N ₁₉ O ₁₄ S
267534	H-D-Arg-	OH	2-thienyl	Me	S	C ₅₂ H ₇₉ N ₁₉ O ₁₃ S ₂

SOURCE – Fournier.

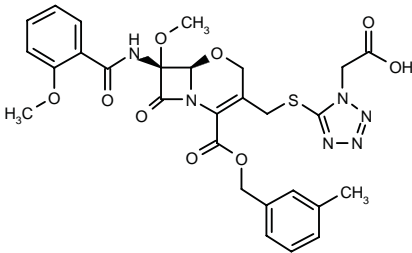
REFERENCES

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B-152

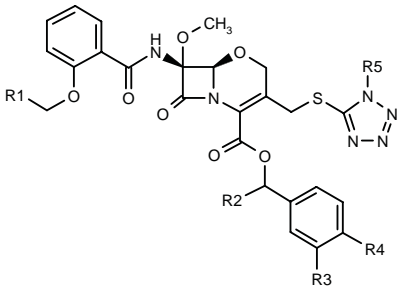
264325

(6*R*,7*R*)-3-[1-(Carboxymethyl)tetrazol-5-ylsulfanylmethyl]-7-methoxy-7-(2-methoxybenzamido)-1-oxa-3-cephem-4-carboxylic acid 3-methylbenzyl ester



C28 H28 N6 O9 S; Mol wt: 624.6282

ACTION – An inhibitor of human chymase (IC₅₀ = 0.006 μM) with potential in the treatment of circulatory disorders, allergy, inflammation, asthma and rheumatism. Within this series of cephem derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
B-66 [267428]	H	Me	Cl	H	CH2CO2H	C ₂₈ H ₂₇ ClN ₆ O ₉ S
B-135 [267429]	H	H	CO2H	H	Me	C ₂₇ H ₂₆ N ₆ O ₉ S
B-136 [267430]	H	H	H	CO2H	Me	C ₂₇ H ₂₆ N ₆ O ₉ S
B-146 [267432]	H	H	Me	H	allyl-OCOCH2	C ₃₁ H ₃₂ N ₆ O ₉ S
B-153 [267433]	Me	H	Me	H	CH2CO2H	C ₂₉ H ₃₀ N ₆ O ₉ S

SOURCE – Shionogi.

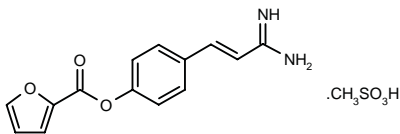
REFERENCES

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BCX-1170

266977

Furan-2-carboxylic acid 4-[3-amino-3-imino-1(*E*)-propen-yl]phenyl ester methanesulfonate



C14 H12 N2 O3 . C H4 O3 S; Mol wt: 352.3654

ACTION – Potent, small-molecule inhibitor of complement, with an IC₅₀ of 240 nM for factor D (alternative pathway) and of 22 nM for C1s (classical pathway), as well as several serine proteases involved in the coagulation cascade. It inhibited the development of the Arthus reaction in rats, inhibited the *ex vivo* activation of the alternative complement pathway (60% at 3 mg/kg/h i.v.) in rats, and prolonged the activated clotting time in human plasma 2-fold at 1 μM. Potentially useful for the treatment of disorders or clinical situations characterized by activation of multiple inflammatory systems such as in cardiopulmonary bypass.

SOURCE – BioCryst.

REFERENCES

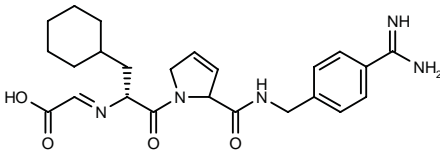
1. Niwas, S. et al. *Development of novel inhibitors of complement and coagulation serine proteases*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 088.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

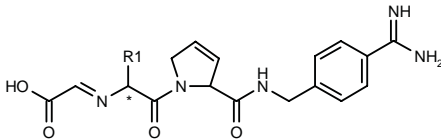
263265

4-[Carboxymethylene-D-cyclohexylanyl-D,L-(3,4-didehydro)prolylaminoethyl]benzamidine



C24 H31 N5 O4; Mol wt: 453.5399

ACTION – Antithrombotic, anticoagulant and anti-inflammatory agent, an inhibitor of serine proteases, particularly thrombin and kininogenases such as kallikrein. Within this series of dipeptide benzamidine derivatives, the following are also included:

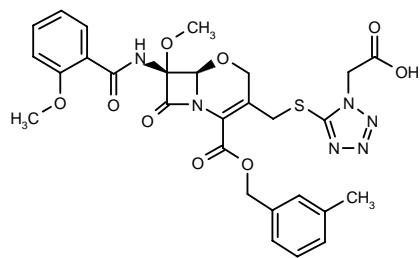


Compound	R1	*Isomer	Formula
266442	cyclohexyl	D	C ₂₃ H ₂₉ N ₅ O ₄
266443	cycloheptyl-CH2	D,L	C ₂₅ H ₃₃ N ₅ O ₄
266444	t-BuCH2	D	C ₂₂ H ₂₉ N ₅ O ₄

B-152

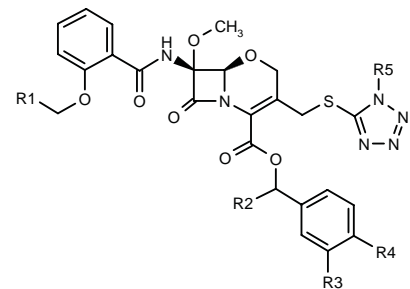
264325

(6*R*,7*R*)-3-[1-(Carboxymethyl)tetrazol-5-ylsulfanylmethyl]-7-methoxy-7-(2-methoxybenzamido)-1-oxa-3-cephem-4-carboxylic acid 3-methylbenzyl ester



C28 H28 N6 O9 S; Mol wt: 624.6282

ACTION – An inhibitor of human chymase (IC₅₀ = 0.006 μM) with potential in the treatment of circulatory disorders, allergy, inflammation, asthma and rheumatism. Within this series of cephem derivatives, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
B-66 [267428]	H	Me	Cl	H	CH2CO2H	C ₂₈ H ₂₇ ClN ₆ O ₉ S
B-135 [267429]	H	H	CO2H	H	Me	C ₂₇ H ₂₆ N ₆ O ₉ S
B-136 [267430]	H	H	H	CO2H	Me	C ₂₇ H ₂₆ N ₆ O ₉ S
B-146 [267432]	H	H	Me	H	allyl-OCOCH2	C ₃₁ H ₃₂ N ₆ O ₉ S
B-153 [267433]	Me	H	Me	H	CH2CO2H	C ₂₉ H ₃₀ N ₆ O ₉ S

SOURCE – Shionogi.

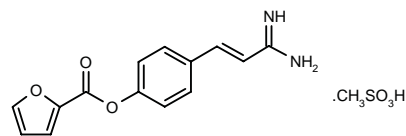
REFERENCES

1. Nishitani, Y. et al. (Shionogi & Co. Ltd.) *Chymase inhibitors containing cephe*ms. JP 98087493.

BCX-1170

266977

Furan-2-carboxylic acid 4-[3-amino-3-imino-1(*E*)-propen-yl]phenyl ester methanesulfonate



C14 H12 N2 O3 . C H4 O3 S; Mol wt: 352.3654

ACTION – Potent, small-molecule inhibitor of complement, with an IC₅₀ of 240 nM for factor D (alternative pathway) and of 22 nM for C1s (classical pathway), as well as several serine proteases involved in the coagulation cascade. It inhibited the development of the Arthus reaction in rats, inhibited the *ex vivo* activation of the alternative complement pathway (60% at 3 mg/kg/h i.v.) in rats, and prolonged the activated clotting time in human plasma 2-fold at 1 μM. Potentially useful for the treatment of disorders or clinical situations characterized by activation of multiple inflammatory systems such as in cardiopulmonary bypass.

SOURCE – BioCryst.

REFERENCES

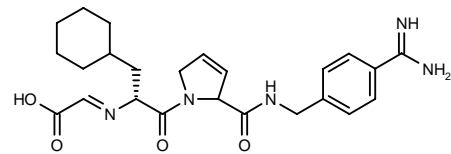
1. Niwas, S. et al. *Development of novel inhibitors of complement and coagulation serine proteases*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 088.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

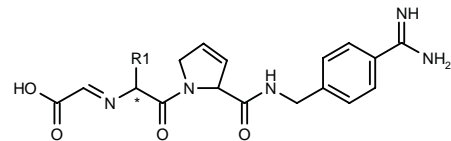
263265

4-[Carboxymethylene-D-cyclohexylanyl-D,L-(3,4-didehydro)prolylaminomethyl]benzamidine

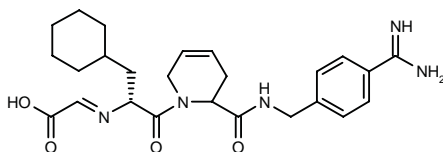


C24 H31 N5 O4; Mol wt: 453.5399

ACTION – Antithrombotic, anticoagulant and anti-inflammatory agent, an inhibitor of serine proteases, particularly thrombin and kininogenases such as kallikrein. Within this series of dipeptide benzamidine derivatives, the following are also included:



Compound	R1	*Isomer	Formula
266442	cyclohexyl	D	C ₂₃ H ₂₉ N ₅ O ₄
266443	cycloheptyl-CH2	D,L	C ₂₅ H ₃₃ N ₅ O ₄
266444	t-BuCH2	D	C ₂₂ H ₂₉ N ₅ O ₄



266445: C₂₅ H₃₃ N₅ O₄

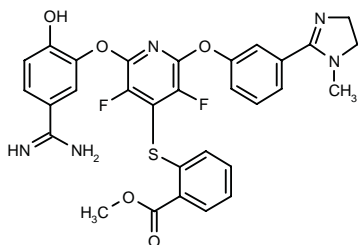
SOURCE – BASF.

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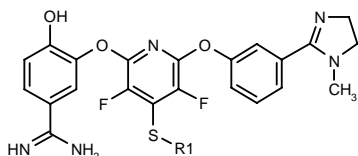
264434

2-[2-(5-Amidino-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyridin-4-ylsulfanyl]benzoic acid methyl ester



C₃₀ H₂₅ F₂ N₅ O₅ S; Mol wt: 605.6195

ACTION – Anticoagulant and antithrombotic agent, a human factor Xa inhibitor. A representative compound from a series of thio acid-derived monocyclic *N*-heterocycles, wherein the following are also specifically claimed:



Compound	R1	Formula
267819	CH ₂ CO ₂ Me	C ₂₅ H ₂₃ F ₂ N ₅ O ₅ S
267820	5-CO ₂ H-2-Pyr	C ₂₈ H ₂₂ F ₂ N ₆ O ₅ S

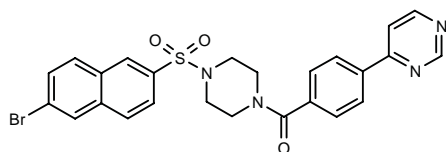
SOURCE – Schering AG.

REFERENCES

1. Kochanny, M.J. et al. (Schering AG) *Thio acid derived monocyclic N-heterocycles as anticoagulants*. WO 9815547.

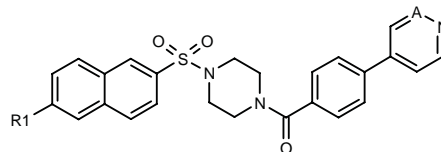
265484

1-(6-Bromonaphthalen-2-ylsulfonyl)-4-[4-(4-pyrimidinyl)-benzoyl]piperazine



C₂₅ H₂₁ Br N₄ O₃ S; Mol wt: 537.4359

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of human factor Xa. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	A	Formula
266602	Cl	CH	C ₂₆ H ₂₂ ClN ₃ O ₃ S
266603	Br	N	C ₂₅ H ₂₁ BrN ₄ O ₃ S

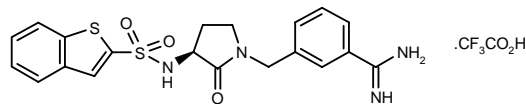
SOURCE – Zeneca.

REFERENCES

1. Preston, J. et al. (Zeneca Ltd.) *Heterocycle derivs. which inhibitor factor Xa*. WO 9821188.

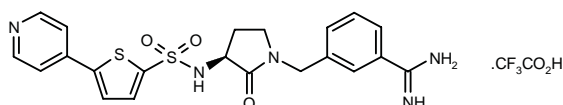
266224

3-[3(*S*)-(Benzo[*b*]thien-2-ylsulfonamido)-2-oxopyrrolidin-1-ylmethyl]benzamidine trifluoroacetate



C₂₀ H₂₀ N₄ O₃ S₂ . C₂ H F₃ O₂; Mol wt: 542.5569

ACTION – Anticoagulant and antithrombotic agent, a potent inhibitor of factor Xa (*K_i* = 14 nM). Another compound from this series of sulfonamidopyrrolidinones is:



267336: C₂₁ H₂₁ N₅ O₃ S₂ . C₂ H F₃ O₂

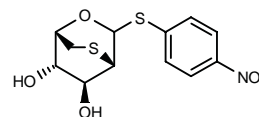
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Ewing, W.R. et al. (Rhône-Poulenc Rorer SA) *Substd. sulfonic acid N-[(aminoiminomethyl)phenylalkyl]-azaheterocyclamide cpds*. WO 9824784.

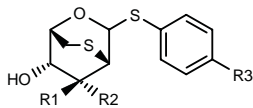
266228

1-*S*-(4-Nitrophenyl) 2,6-anhydro-1,2-dideoxy-1,2-dithio-D-mannopyranoside



C₁₂ H₁₃ N O₅ S₂; Mol wt: 315.3687

ACTION – Orally active anticoagulant and antithrombotic agent, as demonstrated in a venous thrombosis model in rats, where it produced 71% inhibition of thrombus formation when given at 12.5 mg/kg p.o. administered 3 h prior to thrombus induction, compared to 44% inhibition for reference compound becaparil at the same dose. Other specifically claimed compounds from this series of glycosides include the following:



Compound	R1	R2	R3	Formula
267553	H	OH	CN	C ₁₃ H ₁₃ NO ₃ S ₂
267554	OH	H	CN	C ₁₃ H ₁₃ NO ₃ S ₂
267555	OH	H	C(=NH)OMe	C ₁₄ H ₁₇ NO ₄ S ₂
267556	OH	H	CSNH ₂	C ₁₃ H ₁₅ NO ₃ S ₃
267557	OH	H	C(=NH)SMe	C ₁₄ H ₁₇ NO ₃ S ₃
267558	N ₃	H	CN	C ₁₃ H ₁₂ N ₄ O ₂ S ₂
267559	OH	H	C(=NH)NH ₂	C ₁₃ H ₁₆ N ₂ O ₃ S ₂

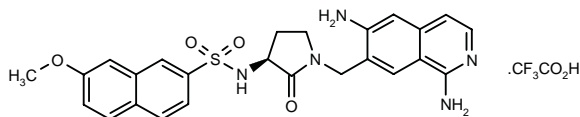
SOURCE – Gedeon Richter.

REFERENCES

1. Kovácsné Bozó, E. et al. (Gedeon Richter) *Anticoagulant glycosides and pharmaceutical compsns. thereof.* WO 9824792.

267646

N-[1-(1,6-Diaminoisoquinolin-7-ylmethyl)-2-oxopyrrolidin-3(*S*)-yl]-7-methoxynaphthalene-2-sulfonamide trifluoroacetate



C₂₅ H₂₅ N₅ O₄ S . C₂ H F₃ O₂; Mol wt: 605.5914

ACTION – Anticoagulant, an inhibitor of factor Xa (K_i = 80 nM).

SOURCE – Rhône-Poulenc Rorer.

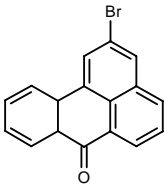
REFERENCES

1. Choi-Sledeski, Y.M. et al. (Rhône-Poulenc Rorer Pharmaceuticals Inc.) *Sulfonic acid or sulfonylamino N-(heteroalkyl)-azaheterocyclamide cpds.* WO 9825611.

ANTIPLATELET THERAPY

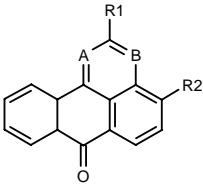
265103

2-Bromo-7a,11a-dihydro-7*H*-benzo[*de*]anthracen-7-one

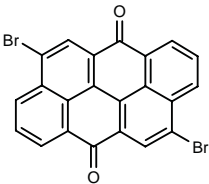


C₁₇ H₁₁ Br O; Mol wt: 311.1769

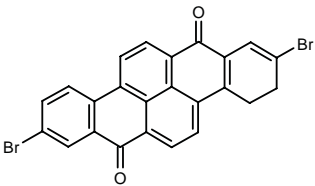
ACTION – Cell adhesion inhibitor that acts as a fibrinogen (gpIIb/IIIa) receptor antagonist and also blocks the binding of endogenous ligands to other integrin receptors. Potentially useful in the treatment of thrombosis, myocardial infarction, coronary disorders, arteriosclerosis, tumors, osteoporosis, inflammatory disorders and microbial infections. Within this series of fused polycyclic compounds, the following are also specifically claimed:



Compound	R1	R2	A	B	Formula
267627	H	NHCH ₂ CH ₂ -OCOOPh	N	N	C ₂₄ H ₁₉ N ₃ O ₄
267628	H	H	CH	C(4-Me-1-Piz)	C ₂₂ H ₂₂ N ₂ O
267629	H	H	CH	C(4-morpholiny)	C ₂₁ H ₁₉ NO ₂
267632	Cl	H	C(CO ₂ Et)	N	C ₁₉ H ₁₄ ClNO ₃



267630: C₂₂ H₈ Br₂ O₂



267631: C₂₄ H₁₂ Br₂ O₂

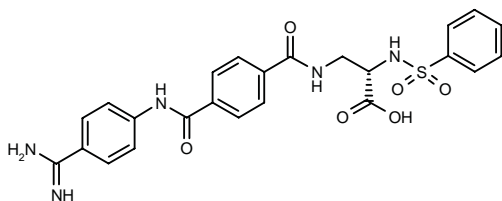
SOURCE – Merck KGaA.

REFERENCES

1. Juraszyk, H. et al. (Merck Patent GmbH) *Dihydrobenzoanthracene, -pyrimidinone or dihydronaphthoquinolinone.* WO 9818764.

267540

3-[4-[N-(4-Amidinophenyl)carbamoyl]benzamido]-2(S)-(phenylsulfonamido)propionic acid



C24 H23 N5 O6 S; Mol wt: 509.5407

ACTION – Platelet aggregation inhibitor, a fibrinogen (gpIIb/IIIa) receptor antagonist. Compound potently inhibited platelet aggregation in an *ex vivo* assay in dogs following oral administration, providing 100% inhibition for 6 h at 0.2 mg/kg p.o.

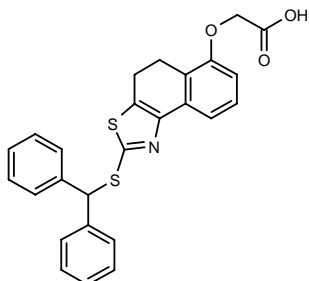
SOURCE – Merck & Co.

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1. Egbertson, M.S. et al. (Merck & Co., Inc.) *Fibrinogen receptor antagonists*. WO 9825601.

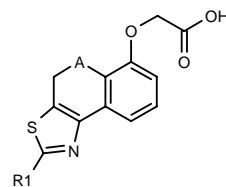
264387

2-[2-(Diphenylmethylsulfanyl)-4,5-dihydronaphtho[1,2-*d*]-thiazol-6-yloxy]acetic acid



C26 H21 N O3 S2; Mol wt: 459.5879

ACTION – Prostaglandin I₂ (PGI₂) receptor agonist, as demonstrated in a binding assay by an IC₅₀ value of 0.002 μM against [³H]-iloprost binding to human PGI₂ receptors cloned in CHO cells. Compound was found to inhibit ADP-induced aggregation of human platelet-rich plasma (PRP) with an IC₅₀ value of 0.21 μM. Claimed for inhibiting platelet aggregation and for the treatment or prevention of transient ischemic attacks, diabetic neuropathy, peripheral vascular diseases or ulcers. Within this series of tricyclic derivatives, the following are also included:



Compound	R1	A	Formula
266473	SCH ₂ CH ₂ CH(Ph) ₂	-O-	C ₂₇ H ₂₃ NO ₄ S ₂
266474	SCH ₂ CH(Ph) ₂	-O-	C ₂₆ H ₂₁ NO ₄ S ₂
266475	SCH ₂ CH(Ph) ₂	-CH ₂ -	C ₂₇ H ₂₃ NO ₃ S ₂
266476	SO ₂ CH ₂ CH(Ph) ₂	-CH ₂ -	C ₂₇ H ₂₃ NO ₅ S ₂

SOURCE – Takeda.

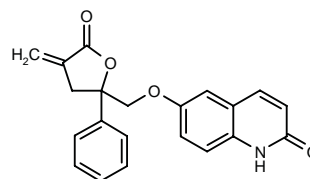
REFERENCES

1. Ohkawa, S. et al. (Takeda Chemical Industries, Ltd.) *Tricyclic cpds. as prostaglandin I₂ receptor agonists*. JP 98152480, WO 9813356.

CCT-62

266324

6-(4-Methylene-5-oxo-2-phenyltetrahydrofuran-2-ylmethoxy)quinolin-2(1*H*)-one



C21 H17 N O4; Mol wt: 347.3683

ACTION – Platelet antiaggregatory agent that inhibits phosphodiesterase type 3 (PDE3) and whose antiplatelet effect is mainly mediated by elevation in cAMP levels. It inhibited rabbit platelet aggregation induced by thrombin, PAF, collagen and arachidonic acid with IC₅₀ values of 18.4 ± 4.5, 10.1 ± 1.6, 3.0 ± 0.9 and 1.5 ± 0.3 μM, respectively, and it also inhibited phosphoinositide breakdown and the increase in intracellular Ca²⁺ concentrations induced by these agonists. Compound also increased intracellular cAMP and cGMP levels in a concentration- and time-dependent manner and inhibited cAMP and cGMP phosphodiesterase (IC₅₀ = 75.0 ± 2.3 and 0.6 ± 0.1 μM, respectively), without affecting adenylate or guanylate cyclase.

SOURCES – Kaohsiung Medical College, Kaohsiung (TW); National Taiwan University, Taipei (TW).

REFERENCES

1. Liao, C.-H. et al. *Cyclic AMP and cyclic GMP phosphodiesterase inhibition by an antiplatelet agent, 6-[(3-methylene-2-oxo-5-phenyl-5-tetrahydrofuran-2-ylmethoxy)quinolinone (CCT-62)]*. Eur J Pharmacol 1998, 349(1): 107.

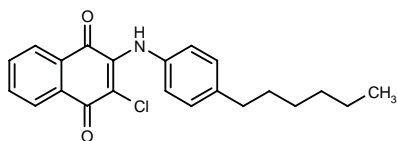
2. Liao, C.H. et al. *Inhibition of platelet activation by a cyclic nucleotide elevating agent, (6-[(3-methylene-2-oxo-5-phenyl-5-tetrahydrofuran-2-ylmethoxy)quinolinone])*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 42.9.

3. Wang, T.-C. et al. *α-Methylidene-γ-butyrolactones. Synthesis and evaluation of quinolin-2(1H)-one derivatives*. Helv Chim Acta 1998, 81(6): 1038.

NQ-304

266321

2-Chloro-3-(4-hexylphenylamino)-1,4-naphthalenedione



C₂₂ H₂₂ Cl N O₂; Mol wt: 367.8738

ACTION – Antithrombotic agent, a platelet aggregation inhibitor proven to inhibit human platelet aggregation induced by ADP, collagen, epinephrine and A23187. Orally administered compound induced dose-dependent inhibition of rat platelet aggregation and protection against pulmonary thrombosis. It appears to act by inhibiting the intracellular pathway leading to gpIIb/IIIa activation via inhibition of TxA₂ synthesis.

SOURCE – Chungbuk National University (KR); Yonsei University (KR).

REFERENCES

1. Yun, Y.P. et al. *The inhibitory effects of 2-chloro-3-[(4-hexylphenyl)-amino]-1,4-naphthalenedione on the platelet aggregation and experimental thrombosis*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.7.

HEMOSTATICS

TR(1-41)

264856

Methionyl-glycyl-prolyl-arginyl-arginyl-leucyl-leucyl-leucyl-valyl-alanyl-alanyl-cysteinyl-phenylalanyl-seryl-leucyl-cysteinyl-glycyl-prolyl-leucyl-leucyl-seryl-alanyl-arginyl-threonyl-arginyl-alanyl-arginyl-arginyl-prolyl-glutamyl-seryl-lysyl-alanyl-threonyl-asparaginyalanyl-threonyl-leucyl-aspartyl-prolyl-arginine

C₁₉₂-H₃₃₀-N₆₄-O₅₃-S₃; Mol wt: 4491.3906

ACTION – Thrombin receptor agonist peptide (TRAP) comprising the first 41 amino acids of the thrombin receptor with potent platelet-activating activity. Also included in the invention are antagonists of and antibodies against the polypeptide for inhibiting TR(1-41)-mediated platelet aggregation or activation.

SOURCE – University of Massachusetts, Boston, MA (US).

REFERENCES

1. Furman, M.I. et al. (University of Massachusetts) *Thrombin receptor peptides and uses thereof*. WO 9816548.

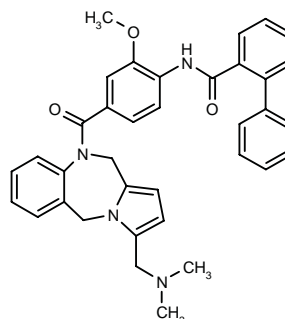
RENAL-UROLOGIC DRUGS

DIURETICS

WAY-140288

266975

N-[4-[3-(Dimethylaminomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-ylcarbonyl]-2-methoxyphenyl]biphenyl-2-carboxamide



C₃₆ H₃₄ N₄ O₃; Mol wt: 570.6896

ACTION – Potent, water-soluble and orally active vasopressin V₂ receptor antagonist with IC₅₀ values of 5.2 and 30.2 nM, respectively, in binding studies using cloned human V₂ receptors expressed in mouse fibroblasts and cloned human V_{1a} receptors in CHO cells. *In vivo*, it dose-dependently increased urine volume after oral administration to water-loaded conscious rats. Potentially useful as an aquaretic for both oral and parenteral administration in the treatment of congestive heart failure and edematous states associated with hyponatremia such as hepatic disease, nephrotic syndrome and renal failure.

SOURCE – Wyeth-Ayerst.

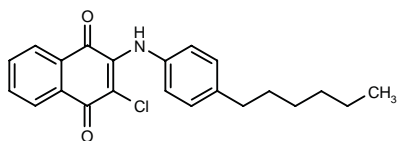
REFERENCES

1. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5700796, WO 9749708.
2. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5753648, WO 9749707.
3. Ashwell, M.A. et al. *The design, synthesis and physicochemical properties of a novel series of human vasopressin-V₂ receptor antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 061.

NQ-304

266321

2-Chloro-3-(4-hexylphenylamino)-1,4-naphthalenedione

C₂₂ H₂₂ Cl N O₂; Mol wt: 367.8738

ACTION – Antithrombotic agent, a platelet aggregation inhibitor proven to inhibit human platelet aggregation induced by ADP, collagen, epinephrine and A23187. Orally administered compound induced dose-dependent inhibition of rat platelet aggregation and protection against pulmonary thrombosis. It appears to act by inhibiting the intracellular pathway leading to gpIIb/IIIa activation via inhibition of TxA₂ synthesis.

SOURCE – Chungbuk National University (KR); Yonsei University (KR).

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HEMOSTATICS

TR(1-41)

264856

Methionyl-glycyl-prolyl-arginyl-arginyl-leucyl-leucyl-leucyl-valyl-alanyl-alanyl-cysteinyl-phenylalanyl-seryl-leucyl-cysteinyl-glycyl-prolyl-leucyl-leucyl-seryl-alanyl-arginyl-threonyl-arginyl-alanyl-arginyl-arginyl-prolyl-glutamyl-seryl-lysyl-alanyl-threonyl-asparaginyal-alanyl-threonyl-leucyl-aspartyl-prolyl-arginine

C₁₉₂-H₃₃₀-N₆₄-O₅₃-S₃; Mol wt: 4491.3906

ACTION – Thrombin receptor agonist peptide (TRAP) comprising the first 41 amino acids of the thrombin receptor with potent platelet-activating activity. Also included in the invention are antagonists of and antibodies against the polypeptide for inhibiting TR(1-41)-mediated platelet aggregation or activation.

SOURCE – University of Massachusetts, Boston, MA (US).

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1. Furman, M.I. et al. (University of Massachusetts) *Thrombin receptor peptides and uses thereof*. WO 9816548.

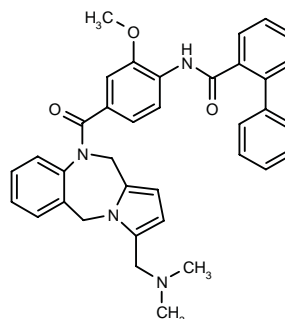
RENAL-UROLOGIC DRUGS

DIURETICS

WAY-140288

266975

N-[4-[3-(Dimethylaminomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10-ylcarbonyl]-2-methoxyphenyl]biphenyl-2-carboxamide

C₃₆ H₃₄ N₄ O₃; Mol wt: 570.6896

ACTION – Potent, water-soluble and orally active vasopressin V₂ receptor antagonist with IC₅₀ values of 5.2 and 30.2 nM, respectively, in binding studies using cloned human V₂ receptors expressed in mouse fibroblasts and cloned human V_{1a} receptors in CHO cells. *In vivo*, it dose-dependently increased urine volume after oral administration to water-loaded conscious rats. Potentially useful as an aquaretic for both oral and parenteral administration in the treatment of congestive heart failure and edematous states associated with hyponatremia such as hepatic disease, nephrotic syndrome and renal failure.

SOURCE – Wyeth-Ayerst.

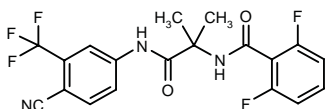
REFERENCES

1. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5700796, WO 9749708.
2. Albright, J.D. et al. (American Cyanamid Co.) *Tricyclic benzazepine vasopressin antagonists*. US 5753648, WO 9749707.
3. Ashwell, M.A. et al. *The design, synthesis and physicochemical properties of a novel series of human vasopressin-V₂ receptor antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 061.

BENIGN PROSTATIC HYPERPLASIA THERAPY

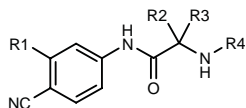
265511

N-[4-Cyano-3-(trifluoromethyl)phenyl]-2-(2,6-difluorobenzamido)-2-methylpropionamide



C₁₉H₁₄F₅N₃O₂; Mol wt: 411.3286

ACTION – Antiandrogenic agent for the treatment of prostatic cancer, prostatic hypertrophy, baldness, acne and seborrhea. *In vivo*, it was shown to inhibit the testosterone-induced increase in prostate weight in castrated juvenile rats (79% inhibition at 10 mg/kg/day p.o. x 5 days). Other related compounds include the following:



Compound	R1	R2	R3	R4	Formula
266572	CF ₃	Me	Me	4-F-PhCO	C ₁₉ H ₁₅ F ₄ N ₃ O ₂
266573	CF ₃	Et	H	4-F-PhSO ₂	C ₁₈ H ₁₅ F ₄ N ₃ O ₃ S
266574	Cl	Me	Me	4-F-PhCO	C ₁₈ H ₁₅ ClF ₃ N ₃ O ₂
266575	CF ₃	Me	Me	2-pyrrolyl-CO	C ₁₇ H ₁₅ F ₃ N ₄ O ₂
266576	CF ₃	Me	Me	2-F-4-Cl-PhCO	C ₁₉ H ₁₄ ClF ₄ N ₃ O ₂

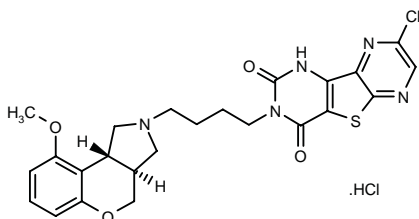
SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, N. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel acylamino-substd. acylanilide derivs. or pharmaceutical compsn. comprising the same.* WO 9822432.

266227

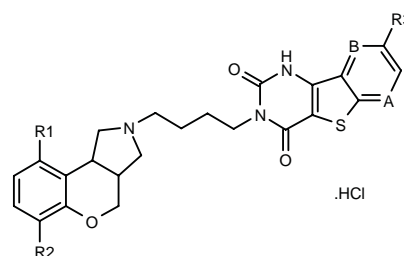
(3a*S*,9b*R*)-*trans*-8-Chloro-3-[4-(9-methoxy-1,2,3,4,9b-hexahydro[1]benzopyrano[3,4-*c*]pyrrol-2-yl)butyl]-pyrazino[2',3':4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride



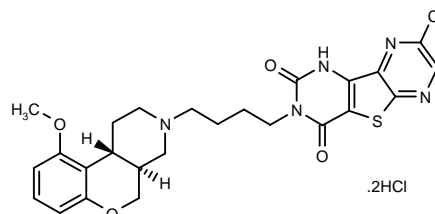
C₂₄H₂₄ClN₅O₄S . HCl; Mol wt: 550.4645

ACTION – Agent for the treatment of benign prostatic hyperplasia (BPH) or other urological diseases such as bladder outlet obstruction and neurogenic bladder, as well as gynecological syndromes such as dysmenorrhea, an α_1 -adrenoceptor antagonist with selectivity for the α_{1a} subtype (bovine; $K_i = 0.041$ nM) over α_{1b} (hamster; $K_i =$

2.49 nM) and α_{1d} (rat; $K_i = 0.112$ nM) subtypes. In functional assays, compound exhibited pA₂ values of 9.8 (rat vas deferens), 8.39 (rat spleen), 9.91 (dog prostate) and 10.39 (rat aorta) for inhibition of phenylephrine-induced contractions. *In vivo*, compound was found to inhibit epinephrine-induced increases in intraurethral pressure in dogs with a pseudo pA₂ value of 8.61 vs. 7.88, 6.91 and 6.90 for prazosin, terazosin and doxazosin, respectively. Compound exhibited weaker hypotensive properties than prazosin, terazosin and doxazosin in a spontaneously hypertensive rat (SHR) model, giving a pED₅₀ value of 6.15 versus pED₅₀ values of 7.4, 6.59 and 6.74 for reference compounds. Other compounds from this series of benzopyranopyrrole and benzopyranopyridine derivatives include the following:



Compound	R1	R2	R3	A	B	Isomer	Formula
267560	MeO	H	MeO	CH	N	3a <i>S</i> ,9b <i>R</i>	C ₂₆ H ₂₈ N ₄ O ₅ S.HCl
267561	MeO	H	Ph	N	N	3a <i>R</i> ,9b <i>R</i>	C ₃₀ H ₂₉ N ₅ O ₄ S.HCl
267562	H	MeO	H	CH	CH	cis	C ₂₄ H ₂₃ N ₃ O ₄ S.HCl



267563: C₂₅H₂₆ClN₅O₄S . 2HCl

SOURCE – Abbott.

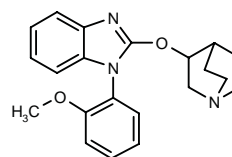
REFERENCES

1. Meyer, M.D. et al. (Abbott Laboratories Inc.) *Benzopyranopyrrole and benzopyranopyridine α -1 adrenergic cpds.* WO 9824791.

TREATMENT OF URINARY INCONTINENCE

264438

1-(2-Methoxyphenyl)-2-(quinuclidin-3-yloxy)benzimidazole



C₂₁H₂₃N₃O₂; Mol wt: 349.4317

ACTION – Agent for the treatment of urinary incontinence, irritable bowel syndrome and asthma with muscarinic receptor-antagonist activity and selectivity for M_1 and M_3 receptors relative to M_2 receptors.

SOURCE – Synthélabo.

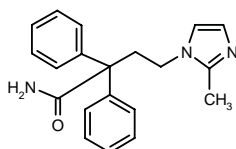
REFERENCES

1. Courtemanche, G. et al. (Synthélabo) *Quinuclidine derivs. as antagonists of muscarinic receptors*. WO 9815551.

KRP-197

266487

4-(2-Methyl-1*H*-imidazolyl-1-yl)-2,2-diphenylbutyramide



C20 H21 N3 O; Mol wt: 319.4059

ACTION – Highly potent and selective M_1 - and M_3 -selective antimuscarinic agent, a representative compound from a series of *N*-substituted 4-amino-2,2-diphenylbutyramide derivatives. It showed K_b values of 0.32, 0.55 and 4.13 nM, respectively, for M_3 (rabbit ileum), M_1 (rabbit vas deferens) and M_2 (guinea pig atria) receptors, giving M_2/M_3 and M_1/M_3 ratios of 13.0 and 1.72, respectively. Selected as a candidate for development in the treatment of urinary incontinence.

SOURCE – Kyorin.

REFERENCES

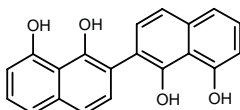
1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Novel imidazole deriv. and process for producing the same*. EP 733621, WO 9515951.
2. Miyachi, H. et al. *Novel imidazole derivatives with subtype-selective antimuscarinic activity (1)*. Bioorg Med Chem Lett 1998, 8(14): 1807.
3. Miyachi, H. et al. *Novel imidazole derivatives with subtype-selective antimuscarinic activity*. 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-09.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

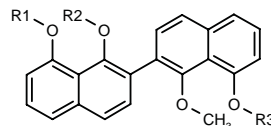
265920

2,2'-Bis(naphthalene-1,8-diol)



C20 H14 O4; Mol wt: 318.3266

ACTION – Antiulcer agent active *in vitro* against *Helicobacter pylori* and also found to possess inhibitory activity against chymotrypsin (70% inhibition of enzyme derived from bovine pancreas at 10 μ M) and cathepsin G (40% inhibition at 10 μ M). Other compounds from this series of binaphthalene derivatives include the following:



Compound	R1	R2	R3	Formula
266595	H	Me	H	C ₂₂ H ₁₈ O ₄
266596	Me	H	H	C ₂₂ H ₁₈ O ₄
266597	Me	Me	Me	C ₂₄ H ₂₂ O ₄
266598	Me	H	Me	C ₂₃ H ₂₀ O ₄

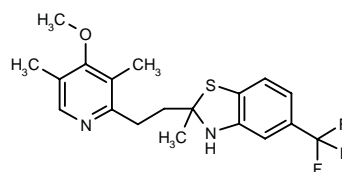
SOURCE – Mitsubishi Chemical.

REFERENCES

1. Kanda, M. et al. (Mitsubishi Chemical Corp.) *Binaphthalene derivs*. JP 98168009.

266492

2-[2-(4-Methoxy-3,5-dimethylpyridin-2-yl)ethyl-2-methyl-5-(trifluoromethyl)-2,3-dihydrobenzothiazole



C19 H21 F3 N2 O S; Mol wt: 382.4479

ACTION – Inhibitor of gastric H^+/K^+ -ATPase ($IC_{50} = 24 \mu$ M) proven to reduce the volume of gastric juice 21% and acid output 38% in rats at a dose of 30 mg/kg p.o. Currently undergoing further evaluation *in vivo*.

SOURCE – Il-Yang.

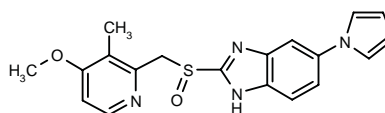
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1. Yoon, S.-H. et al. *Syntheses of 2-[(3,5-dimethyl-4-methoxypyridyl)alkyl]-benzothiazolidine derivatives as a potential gastric H^+/K^+ -ATPase inhibitor*. Bioorg Med Chem Lett 1998, 8(14): 1909.

IY-81149*

228755

2-(4-Methoxy-3-methylpyridin-2-yl)methylsulfinyl)-5-(1-pyrrolyl)-1*H*-benzimidazole



C19 H18 N4 O2 S; Mol wt: 366.4432

ACTION – Agent for the treatment of urinary incontinence, irritable bowel syndrome and asthma with muscarinic receptor-antagonist activity and selectivity for M₁ and M₃ receptors relative to M₂ receptors.

SOURCE – Synthélabo.

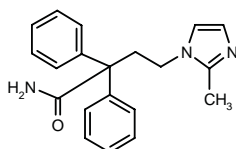
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KRP-197

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SOURCE – Kyorin.

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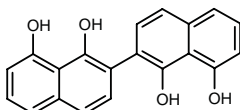
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

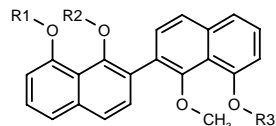
265920

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266596	Me	H	H	C ₂₂ H ₁₈ O ₄
266597	Me	Me	Me	C ₂₄ H ₂₂ O ₄
266598	Me	H	Me	C ₂₃ H ₂₀ O ₄

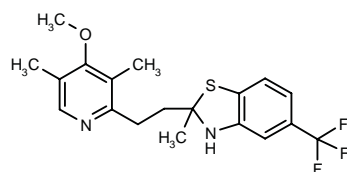
SOURCE – Mitsubishi Chemical.

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266492

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SOURCE – Il-Yang.

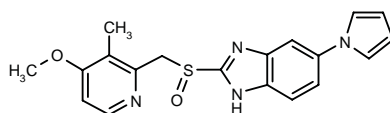
REFERENCES

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IY-81149*

228755

2-(4-Methoxy-3-methylpyridin-2-yl)methylsulfiny)-5-(1-pyrrolyl)-1*H*-benzimidazole



C19 H18 N4 O2 S; Mol wt: 366.4432

ACTION – Antiulcer agent, a proton pump inhibitor with bactericidal effects against *Helicobacter pylori* and a long plasma half-life (17.4 h). Antisecretory effects were demonstrated in pylorus-ligated rats administered doses of 3-30 mg/kg p.o. When given either intraoduodenally (i.d.) or p.o., IY-81149 markedly inhibited indomethacin-, ethanol- and stress-induced gastric lesions in rats with ED₅₀ values of 1.6, 14.2 and 3.6 mg/kg, respectively, and it also inhibited mepirizole-induced duodenal ulcers (ED₅₀ = 10.6 mg/kg) and accelerated healing of acetic acid-induced chronic gastric ulcers when given p.o. b.i.d. for 14 days (ED₅₀ = 5.5 mg/kg). No side effects were observed in a phase I trial.

SOURCE – Il-Yang.

REFERENCES

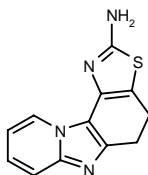
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- Kim, E.J. et al. *The efficacy of IY-81149, a new proton pump inhibitor for the ulcer treatment.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 40.9.

*Identified compound **228755** Drug Data Report 1996, 018(02): 0150.

YJA-20379-5

265971

4,5-Dihydropyrido[1,2-a][1,3]thiazolo[5,4-g]benzimidazol-2-amine



C12 H10 N4 S; Mol wt: 242.3050

ACTION – Antiulcer agent, a proton pump inhibitor giving IC₅₀ values against K⁺-stimulated H⁺/K⁺-ATPase from pig gastric microsomes of 43 and 31 μM, respectively, at pH 6.4 and 7.4 (omeprazole: 20 and 61 μM, respectively). Compound potently inhibited gastric acid secretion in pylorus-ligated rats with an ED₅₀ value of 15.4 mg/kg intraduodenally, and it inhibited water-immersion stress-, indomethacin- and ethanol-induced gastric ulcers and mepirizole-induced duodenal ulcers in rats with ED₅₀ values of 17.6, 4.7, 3.0 and 18.7 mg/kg p.o., respectively. Repeated oral administration (b.i.d. for 8 days) dose-dependently accelerated healing of acetic acid-induced ulcers in rats, with 30.3, 31.6 and 41.9% inhibition, respectively, at doses of 20, 60 and 200 mg/kg/day.

SOURCE – Yung-Jin.

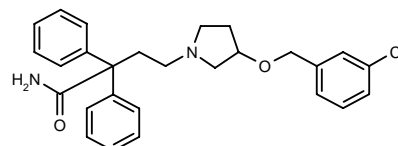
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- Yoo, H.Y. et al. (Yung-Jin Pharmaceutical Co., Ltd.) *Heterocycle-fused thiazole derivs.* EP 843681, JP 98508877, WO 9703076.
- Sohn, S.K. et al. *Biochemical and pharmacological properties of a new proton pump inhibitor, 2-amino-4,5-dihydropyrido[1,2-a][1,3]thiazolo[5,4-g]benzimidazole (YJA20379-5).* Arch Pharmacol Res 1998, 21(3): 241.

IRRITABLE BOWEL SYNDROME THERAPY

266207

4-[3-(3-Chlorobenzoyloxy)pyrrolidin-1-yl]-2,2-diphenylbutyramide



C27 H29 Cl N2 O2; Mol wt: 448.9911

ACTION – Potent and highly selective antagonist of smooth muscle muscarinic receptors with potential in the treatment of irritable bowel syndrome and related disorders. *In vitro*, compound inhibited acetylcholine-induced contractions of guinea pig ileum, rabbit pupilla and guinea pig atrium with pA₂ values of 7.6, 7.3 and 6.2, respectively. When administered orally at 10 mg/kg to rats, it was shown to produce 48.9% inhibition of stress-induced defecation.

SOURCE – Kyorin.

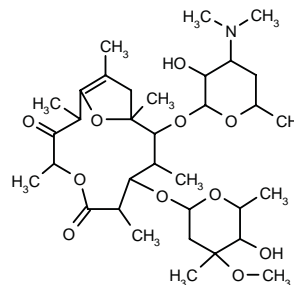
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TREATMENT OF DISORDERS OF GASTRIC EMPTYING

266202

5-[4-(Dimethylamino)-3-hydroxy-6-methyltetrahydropyran-2-yloxy]-6,9-epoxy-3-(5-hydroxy-4-methoxy-4,6-dimethyltetrahydropyran-2-yoxy)-2,4,6,8,10-pentamethyl-11-oxo-8-trideceno-12-lactone



C34 H57 N O11; Mol wt: 655.8203

ACTION – Gastrointestinal prokinetic agent that displays high affinity for the motilin receptor (IC₅₀ = 5.7 nM against [¹²⁵I]-motilin binding to rabbit duodenal preparations).

SOURCE – Chugai.

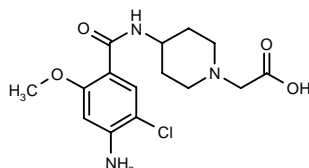
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AU-130^{1,2}

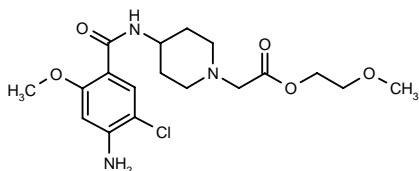
266252

4-(4-Amino-5-chloro-2-methoxybenzamido)piperidine-1-acetic acid



C15 H20 Cl N3 O4; Mol wt: 341.7930

ACTION – Colonic prokinetic agent with potential in the treatment of constipation that appears to exert its action through activation of the cholinergic pathway, including indirect 5-HT₄ receptor activation. The compound produced dose-dependent (0.03-1 mg/kg i.v.) stimulation of high-amplitude propagating contractions (HAPCs) in the colon and defecation in beagle dogs; cisapride had no significant effect on defecation at doses of 0.03-1 mg/kg i.v. or 0.3-3 mg/kg i.d. The effects of AU-130 on defecation were antagonized by atropine, hexamethonium and the 5-HT₄ antagonist SDZ-205-557, but not by the 5-HT₃ receptor antagonist LY-278584. It showed lower affinity than cisapride for the 5-HT₄ receptor (pIC₅₀ = 5.4) in binding studies, and a weak effect on 5-HT₄-mediated relaxation in rat esophagus (pEC₅₀ = 5.7) was observed; no affinity for α- or β-adrenoceptors, 5-HT₁, 5-HT₂, 5-HT₃, opioid μ- or κ-receptors was seen in binding studies. **AU-228** is the orally available 2-methoxyethyl ester.



AU-228 [266251]²: C18 H26 Cl N3 O5

SOURCE – Hokuriku Seiyaku.

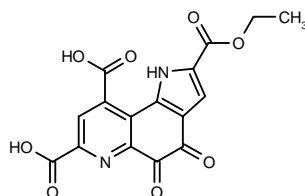
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- Saito, T. et al. *Pharmacological characterization of novel colonic prokinetic agents, AU-130 and AU-228, in conscious dogs*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 40.51.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

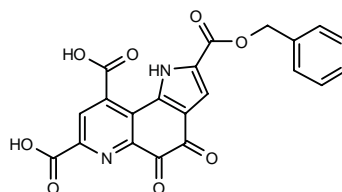
260546

4,5-Dioxo-4,5-dihydro-1H-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylic acid 2-O-ethyl monoester



C16 H10 N2 O8; Mol wt: 358.2610

ACTION – Antioxidant and hepatoprotective agent, a representative compound from a series of pyrroloquinolinequinone derivatives, wherein the following is also included:



266441: C21 H12 N2 O8

SOURCE – Mitsubishi Chemical.

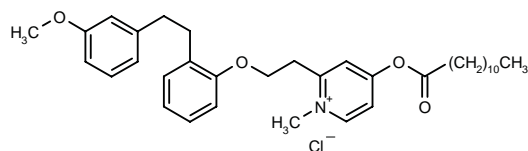
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TREATMENT OF PANCREATIC DISORDERS

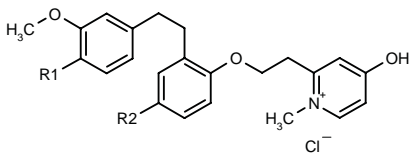
266166

4-(Dodecanoyloxy)-2-[2-[2-(3-methoxyphenyl)-ethyl]phenoxy]ethyl]-1-methylpyridinium chloride



C35 H48 Cl N O4; Mol wt: 582.2202

ACTION – Agent for the treatment or prevention of pancreatitis proven active in a rat model of pancreatitis induced by cerulein, where it dose-dependently reduced serum amylase activity following oral administration of 10, 30 and 100 mg/kg. A representative compound from a series of diarylalkane derivatives, wherein the following are also included:



Compound	R1	R2	Formula
266838	F	F	C ₂₃ H ₂₄ ClF ₂ NO ₃
266839	F	H	C ₂₃ H ₂₅ ClFNO ₃
266840	H	H	C ₂₃ H ₂₆ ClNO ₃

SOURCE – Sankyo.

REFERENCES

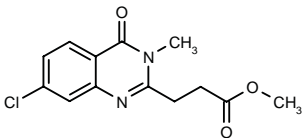
1. Asai, F. and Fujimoto, K. (Sankyo Co., Ltd.) *Compsn. containing diarylalkane deriv. as the active ingredient for treating or preventing pancreatitis*. JP 98212232, WO 9823271.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

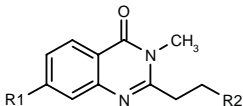
265917

3-(7-Chloro-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)propionic acid methyl ester



C13 H13 Cl N2 O3; Mol wt: 280.7097

ACTION – Hypoglycemic agent, a representative compound from a series of quinazolinone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
266610	Cl	CONHEt	C ₁₄ H ₁₆ ClN ₃ O ₂
266611	Cl	4-morpholinyl- -CH2CH2NHCOCH2CH2	C ₂₀ H ₂₇ ClN ₄ O ₃
266612	F	CH2SMe	C ₁₃ H ₁₅ FN ₂ OS
266613	F	CH2SOMe	C ₁₃ H ₁₅ FN ₂ O ₂ S
266614	F	CH2CH2SOMe	C ₁₄ H ₁₇ FN ₂ O ₂ S
266615	F	CH2CH2SO2Et	C ₁₅ H ₁₉ FN ₂ O ₃ S

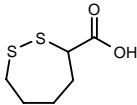
SOURCE – Otsuka.

REFERENCES

1. Kawamura, K. and Kuroki, Y. (Otsuka Pharmaceutical Co., Ltd.) *Quinazolinone derivs*. JP 98158249.

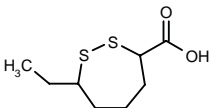
266184

1,2-Dithiepane-3-carboxylic acid

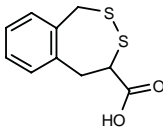


C6 H10 O2 S2; Mol wt: 178.2750

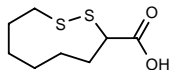
ACTION – Agent for the treatment of diabetic nephropathy, hyperglycemia, hyperlipidemia and gastrointestinal disorders proven to reduce blood urea nitrogen, cholesterol, triglyceride, glucose and urinary albumin in streptozotocin-treated rats following oral administration. A representative compound from a series of cyclic dithio derivatives, wherein the following are also included:



266978: C8 H14 O2 S2



266979: C10 H10 O2 S2



266980: C8 H14 O2 S2

SOURCE – Fuji Chemical.

REFERENCES

1. Kurobe, H. et al. (Fuji Chemical Industry Co., Ltd.) *Cyclic dithio derivs., remedies for diabetic kidney diseases, hypoglycemic agents, hypolipidemic agents, and lenitives for digestive disorders*. WO 9823606.

MIGLITOL

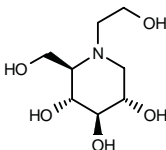
Prop INN; BAN; USAN

102773

1,5-Dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol

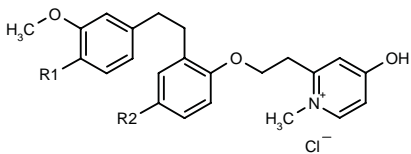
(2R,3R,4R,5S)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol

Bay-m-1099⁺



C8 H17 N O5; Mol wt: 207.2243

ACTION – Antidiabetic agent, an α-glucosidase inhibitor.



Compound	R1	R2	Formula
266838	F	F	C ₂₃ H ₂₄ ClF ₂ NO ₃
266839	F	H	C ₂₃ H ₂₅ ClFNO ₃
266840	H	H	C ₂₃ H ₂₆ ClNO ₃

SOURCE – Sankyo.

REFERENCES

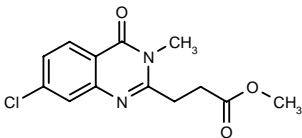
1. Asai, F. and Fujimoto, K. (Sankyo Co., Ltd.) *Compsn. containing diarylalkane deriv. as the active ingredient for treating or preventing pancreatitis*. JP 98212232, WO 9823271.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

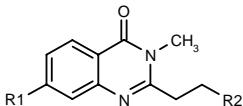
265917

3-(7-Chloro-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)propionic acid methyl ester



C13 H13 Cl N2 O3; Mol wt: 280.7097

ACTION – Hypoglycemic agent, a representative compound from a series of quinazolinone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
266610	Cl	CONHEt	C ₁₄ H ₁₆ ClN ₃ O ₂
266611	Cl	4-morpholinyl- -CH2CH2NHCOCH2CH2	C ₂₀ H ₂₇ ClN ₄ O ₃
266612	F	CH2SMe	C ₁₃ H ₁₅ FN ₂ OS
266613	F	CH2SOMe	C ₁₃ H ₁₅ FN ₂ O ₂ S
266614	F	CH2CH2SOMe	C ₁₄ H ₁₇ FN ₂ O ₂ S
266615	F	CH2CH2SO2Et	C ₁₅ H ₁₉ FN ₂ O ₃ S

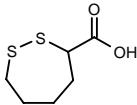
SOURCE – Otsuka.

REFERENCES

1. Kawamura, K. and Kuroki, Y. (Otsuka Pharmaceutical Co., Ltd.) *Quinazolinone derivs*. JP 98158249.

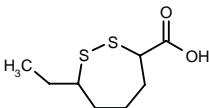
266184

1,2-Dithiepane-3-carboxylic acid

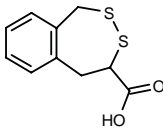


C6 H10 O2 S2; Mol wt: 178.2750

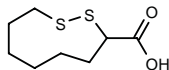
ACTION – Agent for the treatment of diabetic nephropathy, hyperglycemia, hyperlipidemia and gastrointestinal disorders proven to reduce blood urea nitrogen, cholesterol, triglyceride, glucose and urinary albumin in streptozotocin-treated rats following oral administration. A representative compound from a series of cyclic dithio derivatives, wherein the following are also included:



266978: C8 H14 O2 S2



266979: C10 H10 O2 S2



266980: C8 H14 O2 S2

SOURCE – Fuji Chemical.

REFERENCES

1. Kurobe, H. et al. (Fuji Chemical Industry Co., Ltd.) *Cyclic dithio derivs., remedies for diabetic kidney diseases, hypoglycemic agents, hypolipidemic agents, and lenitives for digestive disorders*. WO 9823606.

MIGLITOL

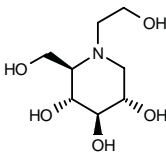
Prop INN; BAN; USAN

102773

1,5-Dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol

(2R,3R,4R,5S)-1-(2-Hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol

Bay-m-1099⁺



C8 H17 N O5; Mol wt: 207.2243

ACTION – Antidiabetic agent, an α-glucosidase inhibitor.

INDICATION – As an adjunct to diet or to diet plus sulfonylurea therapy to improve glycemic control in patients with type II (non-insulin-dependent) diabetes.

PRESENTATION – Tablets, 50 and 100 mg.

PROPRIETARY NAME – *Diastabol* (DE).

SOURCES – Bayer; Sanofi.

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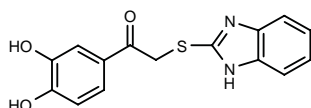
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*Drug Data Rep 1985, 07(03): 0167.

NNC-92-1687

267066

2-(1*H*-Benzimidazol-2-ylsulfanyl)-1-(3,4-dihydroxyphenyl)-1-ethanone



C15 H12 N2 O3 S; Mol wt: 300.3368

ACTION – Nonpeptide, competitive human glucagon receptor antagonist ($K_i = 9.1 \mu\text{M}$, $\text{IC}_{50} = 20 \mu\text{M}$).

SOURCE – Novo Nordisk.

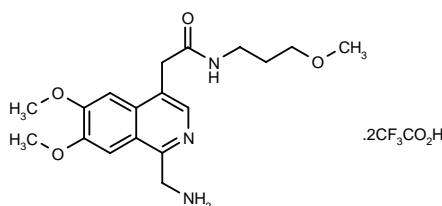
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SDZ-274444

267150

2-[1-(Aminomethyl)-6,7-dimethoxy-4-isoquinolinyl]-*N*-(3-methoxypropyl)acetamide bis(trifluoroacetate)



C18 H25 N3 O4 . 2 C2 H F3 O2; Mol wt: 575.4563

ACTION – Inhibitor of human epithelial cell dipeptidyl peptidase IV (DPP-IV; $\text{IC}_{50} = 5.4 \mu\text{M}$) from a series of 1,4-disubstituted isoquinoline-based amino amides.

SOURCE – Novartis.

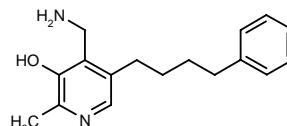
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TREATMENT OF DIABETIC COMPLICATIONS

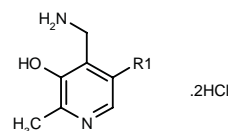
265933

4-(Aminomethyl)-3-hydroxy-2-methyl-5-(4-phenylbutyl)-pyridine



C17 H22 N2 O; Mol wt: 270.3738

ACTION – Maillard reaction inhibitor (93.7% inhibition at 0.2 mM), a representative compound from a series of 4-aminomethyl-3-hydroxypyridine derivatives, wherein the following are also included:



Compound	R1	Formula
266531	CH2CH2CO2Et	C ₁₂ H ₁₈ N ₂ O ₃ ·2HCl
266532	CH2CH2CONH2	C ₁₀ H ₁₅ N ₃ O ₂ ·2HCl
266533	CH(OH)C9H19	C ₁₇ H ₃₀ N ₂ O ₂ ·2HCl

SOURCE – Kissei.

REFERENCES

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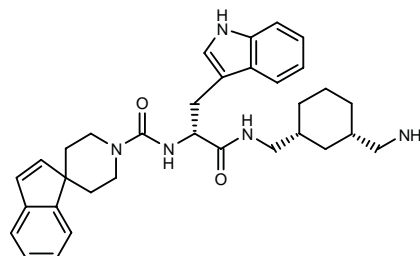
TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

L-054264

265668

N-(Spiro[indene-1,4'-piperidin]-1'-ylcarbonyl)-*D*-tryptophan 3(*S*)-(aminomethyl)-1(*R*)-cyclohexylmethylamide

N-[2-[3(*S*)-(Aminomethyl)-1(*R*)-cyclohexylmethylamino]-1(*R*)-(1*H*-indol-3-ylmethyl)-2-oxoethyl]spiro[1*H*-indene-1,4'-piperidine]-1'-carboxamide



C33 H41 N5 O2; Mol wt: 539.7199

ACTION – The first potent, selective, small-molecule somatostatin sst2 receptor agonist reported ($K_i = 1.6$ nM; K_i sst1, sst3, sst4 and sst5 receptors = 1740, 2950, 2000 and 4470 nM, respectively), with full agonist activity in a functional assay of inhibition of forskolin-stimulated cAMP accumulation in stably transfected mouse L20ZZH cells ($IC_{50} = 2$ nM) and of inhibition of growth hormone release in the rat pituitary cell assay ($IC_{50} = 6$ nM). Potentially useful in the treatment of acromegaly, diabetes, cancer, rheumatoid arthritis and Alzheimer's disease, among other disorders.

SOURCE – Merck & Co.

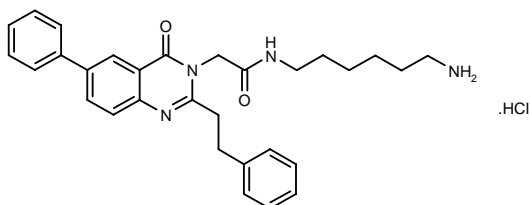
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1. Yang, L. et al. *Spiro[1H-indene-1,4'-piperidine] derivatives as potent and selective non-peptide human somatostatin receptor subtype 2 (sst2) agonists*. J Med Chem 1998, 41(13): 2175.

L-168721

267146

N-(6-Aminohexyl)-2-[6-phenyl-2-(2-phenylethyl)-4-oxo-3,4-dihydro-3-quinazolinyl]acetamide hydrochloride



C30 H34 N4 O2 . HCl; Mol wt: 519.0855

ACTION – Nonpeptide growth hormone secretagogue, a human GH secretagogue receptor (hGHSr) agonist ($IC_{50} = 16$ nM for displacement of radiolabeled MK-0677 from the cloned hGHSr) with high potency in the cultured rat pituitary cell assay ($EC_{50} = 0.5$ nM).

SOURCE – Merck & Co.

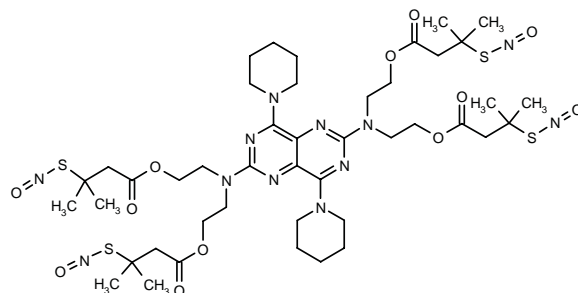
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TREATMENT OF MALE SEXUAL DYSFUNCTION

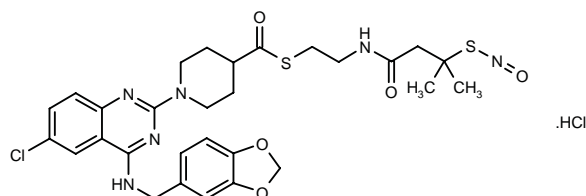
265455

2,6-Bis[*N,N*-bis[2-[3-methyl-3-(nitrososulfanyl)butyryloxy]ethyl]amino]-4,8-di(1-piperidinyl)pyrimido[5,4-*d*]pyrimidine



C44 H68 N12 O12 S4; Mol wt: 1085.357

ACTION – Agent for the treatment of male impotence, a nitrosated derivative of dipyridamole shown to be more effective than dipyridamole in relaxing phenylephrine-induced contractions of human corpus cavernosum tissue at 10 and 30 μ M. Another compound from this broad series of nitrosated and nitrosylated phosphodiesterase (PDE) inhibitors is:



267823: C29 H33 Cl N6 O5 S2 . HCl

SOURCE – NitroMed.

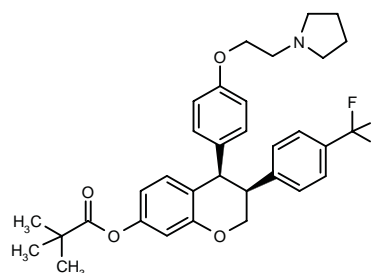
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TREATMENT OF GYNECOLOGICAL DISORDERS

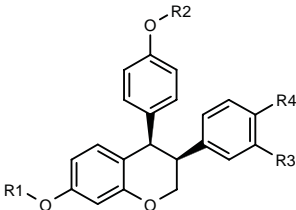
265107

Pivalic acid *cis*-4-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-3-[4-(trifluoromethyl)phenyl]-3,4-dihydro-2*H*-1-benzopyran-7-yl ester



C33 H36 F3 N O4; Mol wt: 567.6444

ACTION – Estrogen agonist with potential in the treatment of estrogen-related disorders, particularly bone loss, osteoporosis, cardiovascular diseases, cognitive disorders, senile dementia, menopausal symptoms, dysmenorrhea, preterm labor, acne, hirsutism, depression, mania, schizophrenia, incontinence, obesity and prostatic carcinoma, and as a contraceptive agent. Compound is reported to act as an antiestrogenic in breast and colon tissue and is thus also potentially useful for the treatment or prevention of estrogen-dependent cancers such as breast and colon cancer. Other compounds from this series of *cis*-3,4-chroman derivatives include the following:



Compound	R1	R2	R3	R4	Formula
268268	t-BuCO	1-pyrrolidinyl- -CH2CH2	CF3	H	C ₃₃ H ₃₆ F ₃ NO ₄
268269	CON(Et)2	1-pyrrolidinyl- -CH2CH2	H	Me	C ₃₃ H ₄₀ N ₂ O ₄
268270	SO2N(Et)2	1-pyrrolidinyl- -CH2CH2	H	Me	C ₃₂ H ₄₀ N ₂ O ₅ S
268271	CH2Ph	H	H	H	C ₂₈ H ₂₄ O ₃
268272	CH2Ph	(CH2)4Cl	H	H	C ₃₂ H ₃₁ ClO ₃
268273	CH2Ph	CH2CH2Cl	H	H	C ₃₀ H ₂₇ ClO ₃
268274	CH2Ph	(CH2)6Br	H	H	C ₃₄ H ₃₆ BrO ₃

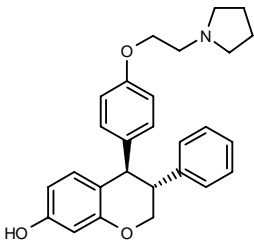
SOURCE – Novo Nordisk.

REFERENCES

1. Jacobsen, P. et al. (Novo Nordisk A/S) *Novel cis-3,4-chroman derivs. useful in the prevention or treatment of estrogen related diseases or syndromes.* WO 9818773.

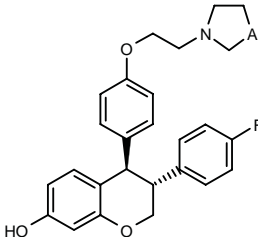
265108

trans-3-Phenyl-4-[2-(1-pyrrolidinyl)ethoxy]-3,4-dihydro-2*H*-1-benzopyran-7-ol



C27 H29 N O3; Mol wt: 415.5301

ACTION – Estrogen agonist with potential in the treatment of estrogen-related disorders such as osteoporosis, cardiovascular diseases, cognitive disorders, menopausal symptoms, dysmenorrhea, preterm labor, acne, hirsutism, depression, mania, schizophrenia, incontinence, obesity and prostatic carcinoma, as well as for contraception. Compound is reported to act as an estrogen in bone and cardiovascular tissues and as an antiestrogen in breast and colon tissue, and is thus also potentially useful for the treatment or prevention of estrogen-dependent cancers such as breast and colon cancer. Other compounds from this series of *trans*-3,4-chroman derivatives include the following:



Compound	A	Formula
266636	-CH2-	C ₂₇ H ₂₈ FNO ₃
266637	-(CH2)2-	C ₂₈ H ₃₀ FNO ₃

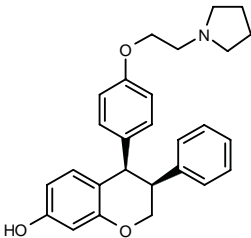
SOURCE – Novo Nordisk.

REFERENCES

1. Jacobsen, P. et al. (Novo Nordisk A/S) *Novel trans-3,4-chroman derivs. useful in the prevention or treatment of estrogen related diseases or syndromes.* WO 9818774.

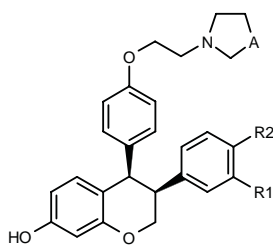
265110

cis-3-Phenyl-4-[2-(1-pyrrolidinyl)ethoxy]-3,4-dihydro-2*H*-1-benzopyran-7-ol



C27 H29 N O3; Mol wt: 415.5301

ACTION – Estrogen agonist with potential in the treatment of estrogen-related disorders, particularly bone loss, osteoporosis, cardiovascular diseases, cognitive disorders, senile dementia, menopausal symptoms, dysmenorrhea, preterm labor, acne, hirsutism, depression, mania, schizophrenia, incontinence, obesity and prostatic carcinoma, and as a contraceptive agent. Compound is reported to act as an antiestrogenic in breast and colon tissue and is thus also potentially useful for the treatment or prevention of estrogen-dependent cancers such as breast and colon cancer. Other compounds from this series of *cis*-3,4-chroman derivatives include the following:



Compound	R1	R2	A	Formula
268275	H	H	-CH2-	C ₂₇ H ₂₉ NO ₃
268276	H	H	-CH2-	C ₂₇ H ₂₉ NO ₃
268277	CF ₃	H	-CH2-	C ₂₈ H ₂₈ F ₃ NO ₃
268278	Me	H	-CH2-	C ₂₈ H ₃₁ NO ₃
268279	H	OH	-CH2-	C ₂₇ H ₂₉ NO ₄
268280	F	H	-CH2-	C ₂₇ H ₂₈ FNO ₃
268281	F	H	-(CH ₂) ₂ -	C ₂₈ H ₃₀ FNO ₃

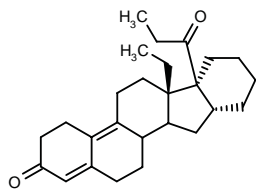
SOURCE – Novo Nordisk.

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1. Jacobsen, P. et al. (Novo Nordisk A/S) *Novel cis-3,4-chroman derivs. useful in the prevention or treatment of estrogen related diseases or syndromes.* WO 9818776.

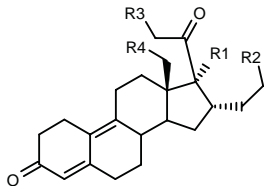
266204

13β-Ethyl-17β-propionyl-16β,17β,3',4',5',6'-hexahydrobenzo[16,17]gona-4,9-dien-3-one



C26 H36 O2; Mol wt: 380.5684

ACTION – Agent with high progestogenic efficacy and potential in the treatment of gynecological disorders, particularly premenstrual syndrome, as well as for use in hormone replacement therapy or as a contraceptive, optionally in combination with estrogens. Within this series of specifically claimed cycloalkyl steroids, the following are also included:



Compound	R1,R2	R3	R4	Formula
267310	-CH=CH-	Me	H	C ₂₅ H ₃₂ O ₂
267311	-CH=CH-	Me	Me	C ₂₆ H ₃₄ O ₂
267312	-(CH ₂) ₂ -	Me	H	C ₂₅ H ₃₄ O ₂
267313	-CH=CH-	H	H	C ₂₄ H ₃₀ O ₂
267314	-CH=CH-	H	Me	C ₂₅ H ₃₂ O ₂

SOURCE – Schering AG.

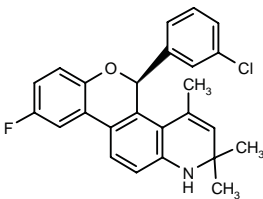
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(S)-LG-120746

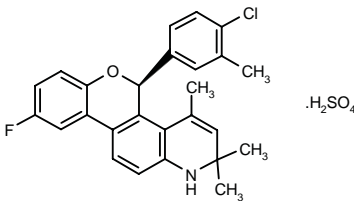
266299

(S)-5-(3-Chlorophenyl)-9-fluoro-2,2,4-trimethyl-2,5-dihydro-1H-[1]benzopyrano[3,4-f]quinoline



C25 H21 Cl F N O; Mol wt: 405.8979

ACTION – Potent, orally active nonsteroidal progesterone receptor agonist, as demonstrated in a binding assay (K_i = 0.1 nM using baculovirus-expressed human progesterone receptor isoform A) and in a cotransfection assay (EC₅₀ = 1.3 nM in CV-1 cells cotransfected with human progesterone receptor isoform B). It displayed potent progesterone-like effects *in vivo*, inhibiting the estrogen-induced increase in uterine wet weight in immature rats and completely restoring pregnancy in mifepristone (RU-486)-treated female mice at oral doses of 1.0 and 3.0 mg/day; in these assays it was more potent than medroxyprogesterone acetate. It was significantly less active than the reference compound in the mammary bud assay in rats, suggesting tissue-selective effects. It may thus represent a safer alternative in hormone replacement therapy (HRT) or for cancers of the female reproductive system. Another nonsteroidal compound with a similar profile is:



266300: C26 H23 Cl F N O . H2 S O4

SOURCE – Ligand.

REFERENCES

1. Jones, T.K. et al. (Ligand Pharmaceuticals, Inc.) *Steroid receptor modulator cpds. and methods.* EP 800519, US 5688808, US 5688810, US 5693646, US 5693647, US 5696127, US 5696130, US 5696133, WO 9619458.

2. Edwards, J.P. et al. *Preparation, resolution, and biological evaluation of 5-aryl-1,2-dihydro-5H-chromeno[3,4-f]quinolines: Potent, orally active, nonsteroidal progesterone receptor agonists.* J Med Chem 1998, 41(15): 2779.

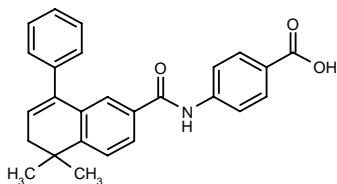
DERMATOLOGIC DRUGS

ACNE THERAPY

BMS-185411*

227124

4-(5,5-Dimethyl-8-phenyl-5,6-dihydronaphthalen-2-ylcarboxamido)benzoic acid



C26 H23 N O3; Mol wt: 397.4717

ACTION – Retinoid that acts as a retinoic acid receptor (RAR) RAR α receptor antagonist (IC_{50} = ~400 nM) and as an agonist at RAR β receptors (EC_{50} = 34 nM) in transactivation assays in transfected HeLa cells. Claimed in patent literature as useful for the treatment of skin disorders such as acne and psoriasis, as well as in the treatment of tumors.

SOURCE – Bristol-Myers Squibb.

REFERENCES

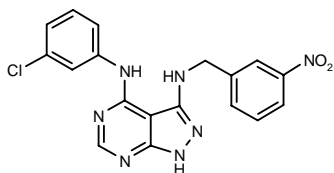
1. Starrett, J.E. Jr. et al. (Bristol-Myers Squibb Co.) *Substd. (5,6)-dihydronaphthalenyl cpds. having retinoid-like activity*. CA 2138000, EP 661259, JP 95242591, US 5648385.
2. Ostrowski, J. et al. *Serine 232 and methionine 272 define the ligand binding pocket in retinoic acid receptor subtypes*. J Biol Chem 1998, 273(6): 3490.
3. Zusi, F.C. et al. *Design, synthesis, and structure-activity relationships for receptor-selective retinoids*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 375.

*Identified compound **227124** Drug Data Report 1995, 017(11): 1021.

ANTIPSORIATICS

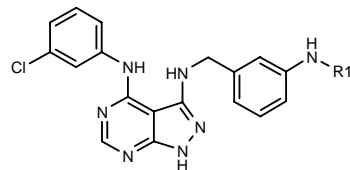
264414

4-(3-Chlorophenylamino)-3-(3-nitrobenzylamino)-1H-pyrazolo[3,4-d]pyrimidine



C18 H14 Cl N7 O2; Mol wt: 395.8086

ACTION – Inhibitor of epidermal growth factor (EGF) receptor protein tyrosine kinase potentially useful for the treatment of hyperproliferative disorders such as psoriasis and cancer. Other specifically claimed compounds from this series of fused pyrazole derivatives include the following:



Compound	R1	Formula
266439	t-BuOCO	C ₂₃ H ₂₄ ClN ₇ O ₂
266440	Me	C ₁₉ H ₁₈ ClN ₇

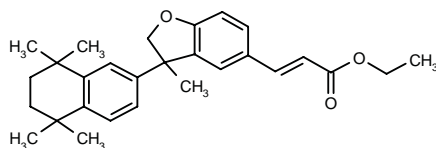
SOURCE – Novartis.

REFERENCES

1. Bold, G. et al. (Novartis AG) *Fused pyrazole derivs. and processes for their preparation*. WO 9814449, WO 9814451.

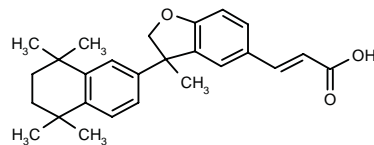
266220

3-[3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-2,3-dihydrobenzofuran-5-yl]-2(E)-propenoic acid ethyl ester



C28 H34 O3; Mol wt: 418.5736

ACTION – Agent for the treatment of skin disorders including psoriasis, acne, ichthyoses and other keratinization and hyperproliferative disorders with retinoic acid receptor (RAR)- and/or retinoid X receptor (RXR)-modulating activity. Another specifically claimed compound from this series of benzofuran-acrylic acid derivatives is:



267448: C26 H30 O3

SOURCE – Galderma.

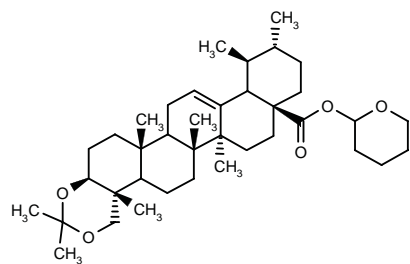
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1. Diaz, P. and Charpentier, B. (CIRD Galderma) *Benzofuran-acrylic acid derivs. and their use as modulators of RXRS or RARS receptors*. EP 882033, WO 9824778.

WOUND-HEALING AGENTS

266170

[4a *R*-(4a α ,6a α ,6b β ,8a α ,11 β ,12 α ,14b α ,16a β)]-2,2,4a,6a,6b,11,12,14b-Octamethyl-4a,4b,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b,15,16,16a-icosahydro-4*H*-piceno[3,4-*d*]-1,3-dioxin-8a-carboxylic acid tetrahydro-pyran-2-yl ester



C38 H60 O5; Mol wt: 596.8870

ACTION – Wound-healing agent, a derivative of asiatic acid that exhibits higher wound-healing activity in a rat model than titrated extracts of *Centella asiatica* (TECA), the main component of commercially available madecassol ointment, following topical administration.

SOURCE – Dong Kook.

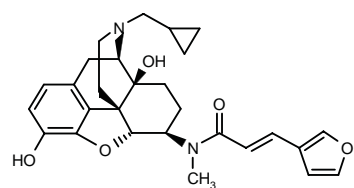
REFERENCES

1. Jew, S.S. et al. (Dong Kook Pharmaceutical Co., Ltd.) *Asiatic acid derivs. and medicines for treating wounds, which contains the same.* WO 9823574.

MISCELLANEOUS DERMATOLOGIC DRUGS

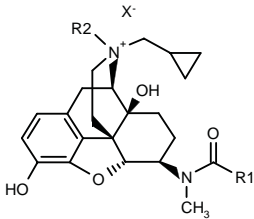
266168

N-[*N*-(Cyclopropylmethyl)-4,5(*R*)-epoxy-3,14-dihydro-xymorphinan-6(*R*)-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide



C28 H32 N2 O5; Mol wt: 476.5698

ACTION – Antipruritic agent with κ -opioid receptor-agonist activity; it produced 58% inhibition of compound 48/80-induced scratching in mice at 0.005 mg/kg s.c. Other related compounds include the following:



Compound	R1	R2	X ⁻	Formula
266841	(E)-3-furyl-CH=CH	Me	iodide	C ₂₉ H ₃₅ IN ₂ O ₅
266842	(E)-3-MeO-PhCH=CH	Me	iodide	C ₃₂ H ₃₅ IN ₂ O ₅
266843	(E)-3-furyl-CH=CH	O ⁻		C ₂₈ H ₃₂ N ₂ O ₆
266844	(E)-3-MeO-PhCH=CH	O ⁻		C ₃₁ H ₃₆ N ₂ O ₆
266845	4-CF3-Ph-ethynyl	O ⁻		C ₃₁ H ₃₁ F ₃ N ₂ O ₅
266846	3-Me-Ph-ethynyl	O ⁻		C ₃₁ H ₃₄ N ₂ O ₅

SOURCE – Toray.

REFERENCES

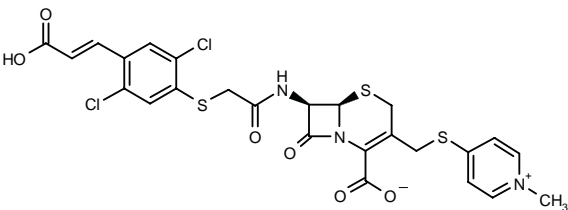
1. Nagase, H. et al. (Toray Industries, Inc.) *Antipruritic agent.* WO 9823290.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

266199

(6*R*,7*R*)-7-[2-[4-[2(*E*)-Carboxyvinyl]-2,5-dichlorophenyl-sulfanyl]acetamido]-3-(1-methylpyridinium-4-ylsulfanyl-methyl)-3-cephem-4-carboxylate



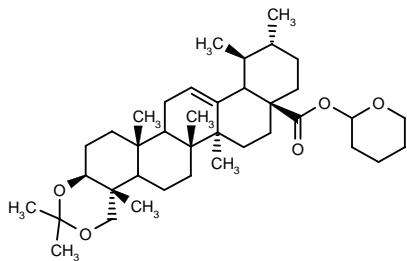
C25 H21 Cl2 N3 O6 S3; Mol wt: 626.5599

ACTION – Cephalosporin antibiotic active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). Other specifically claimed compounds from this series of cephem derivatives include the following:

WOUND-HEALING AGENTS

266170

[4a *R*-(4a α ,6a α ,6b β ,8a α ,11 β ,12 α ,14b α ,16a β)]-2,2,4a,6a,6b,11,12,14b-Octamethyl-4a,4b,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b,15,16,16a-icosahydro-4*H*-piceno[3,4-*d*]-1,3-dioxin-8a-carboxylic acid tetrahydro-pyran-2-yl ester



C38 H60 O5; Mol wt: 596.8870

ACTION – Wound-healing agent, a derivative of asiatic acid that exhibits higher wound-healing activity in a rat model than titrated extracts of *Centella asiatica* (TECA), the main component of commercially available madecassol ointment, following topical administration.

SOURCE – Dong Kook.

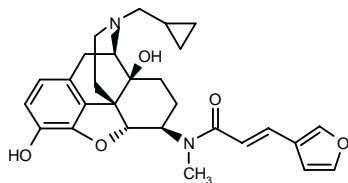
REFERENCES

1. Jew, S.S. et al. (Dong Kook Pharmaceutical Co., Ltd.) *Asiatic acid derivs. and medicines for treating wounds, which contains the same*. WO 9823574.

MISCELLANEOUS DERMATOLOGIC DRUGS

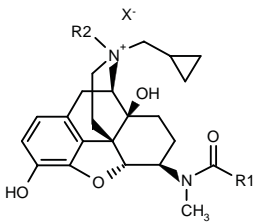
266168

N-[*N*-(Cyclopropylmethyl)-4,5(*R*)-epoxy-3,14-dihydro-xymorphinan-6(*R*)-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide



C28 H32 N2 O5; Mol wt: 476.5698

ACTION – Antipruritic agent with κ -opioid receptor-agonist activity; it produced 58% inhibition of compound 48/80-induced scratching in mice at 0.005 mg/kg s.c. Other related compounds include the following:



Compound	R1	R2	X ⁻	Formula
266841	(E)-3-furyl-CH=CH	Me	iodide	C ₂₉ H ₃₅ IN ₂ O ₅
266842	(E)-3-MeO-PhCH=CH	Me	iodide	C ₃₂ H ₃₅ IN ₂ O ₅
266843	(E)-3-furyl-CH=CH	O ⁻		C ₂₈ H ₃₂ N ₂ O ₆
266844	(E)-3-MeO-PhCH=CH	O ⁻		C ₃₁ H ₃₆ N ₂ O ₆
266845	4-CF3-Ph-ethynyl	O ⁻		C ₃₁ H ₃₁ F ₃ N ₂ O ₅
266846	3-Me-Ph-ethynyl	O ⁻		C ₃₁ H ₃₄ N ₂ O ₅

SOURCE – Toray.

REFERENCES

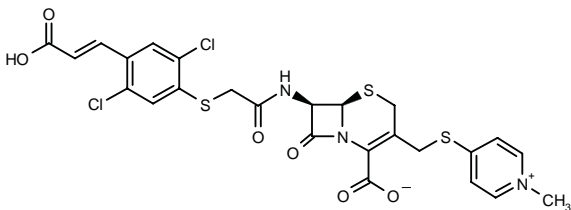
1. Nagase, H. et al. (Toray Industries, Inc.) *Antipruritic agent*. WO 9823290.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

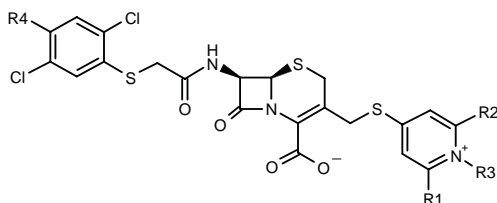
266199

(6*R*,7*R*)-7-[2-[4-[2(*E*)-Carboxyvinyl]-2,5-dichlorophenyl-sulfanyl]acetamido]-3-(1-methylpyridinium-4-ylsulfanyl-methyl)-3-cephem-4-carboxylate



C25 H21 Cl2 N3 O6 S3; Mol wt: 626.5599

ACTION – Cephalosporin antibiotic active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). Other specifically claimed compounds from this series of cephem derivatives include the following:



Compound	R1=R2	R3	R4	Formula
267088	H	NH2	SCH2CO2H	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₆ S ₄
267089	H	NH2	CH=CHCO2H	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₆ S ₃
267090	H	4-Me-4-morpho- linyl-(CH2)3	CH=CHCOO ⁻	C ₃₂ H ₃₄ Cl ₂ N ₄ O ₆ S ₃
267091	Me	NH2	CH=CHCONH- CH2CH2CO2H	C ₂₉ H ₂₉ Cl ₂ N ₅ O ₇ S ₃
267092	Me	4-Me-4-morpho- linyl-(CH2)3	CH=CHCONH- CH2CH2COO ⁻	C ₃₇ H ₄₃ Cl ₂ N ₅ O ₆ S ₃

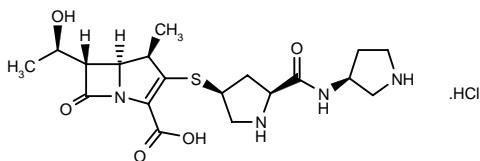
SOURCE – Bristol-Myers Squibb.

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1. Springer, D.M. et al. (Bristol-Myers Squibb Co.) *Cephalosporin derivs.* WO 9823621.

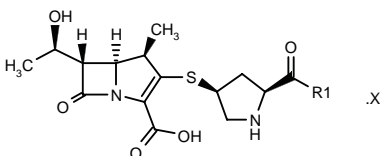
265923

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*S*)-[*N*-[3(*S*)-pyrrolidinyl]carbonyl]pyrrolidin-3(*S*)-ylsulfanyl]-1-carba-2-penam-3-carboxylic acid hydrochloride



C₁₉ H₂₈ N₄ O₅ S . HCl; Mol wt: 460.9801

ACTION – Carbapenem antibiotic, a representative compound from a series of 1-methyl-2-pyrrolidinylsulfanyl-carbapenem derivatives, wherein the following are also included:



Compound	R1	X	Formula
268282	1-(NH=CH)-3(S)-pyrrolidinyl-NH		C ₂₀ H ₂₉ N ₅ O ₅ S
268283	1-[NH=C(Me)]-3(S)-pyrrolidinyl-NH		C ₂₁ H ₃₁ N ₅ O ₅ S
268284	1-(NH=CH)-3(R)-pyrrolidinyl-NH		C ₂₀ H ₂₉ N ₅ O ₅ S
268285	1-(NH=CH)-3(S)-pyrrolidinyl-N(Me)	HCl	C ₂₁ H ₃₁ N ₅ O ₅ S .HCl
268286	3(S)-(1-imidazolyl)-1-pyrrolidinyl	HCl	C ₂₂ H ₂₉ N ₅ O ₅ S .HCl
268287	3(S)-(1,2,4-triazol-1-yl)-1-pyrrolidinyl	HCl	C ₂₁ H ₂₈ N ₆ O ₅ S .HCl

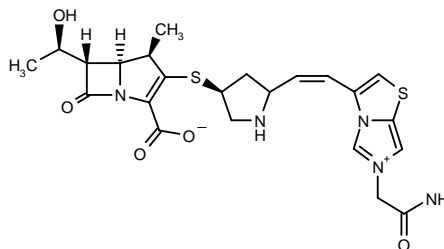
SOURCE – Sankyo.

REFERENCES

1. Kawamoto, I. et al. (Sankyo Co., Ltd.) *1-Methylcarbapenem derivs.* JP 98168081.

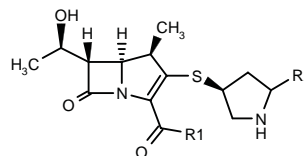
266200

(1*R*,5*S*,6*S*)-2-[5-[2-(*Z*)-[6-(Carbamoylmethyl)imidazo-[5,1-*b*]thiazolium-3-yl]vinyl]pyrrolidin-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate



C23 H27 N5 O5 S2; Mol wt: 517.6283

ACTION – Carbapenem antibiotic with potent *in vitro* activity against a broad range of Gram-positive and Gram-negative bacteria including resistant microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), and reported to possess high stability to dehydropeptidase type I (DHP-I). Compound exhibited MIC values of < 0.025, 3.13, < 0.025 and 1.56 µg/ml when tested against *S. aureus* 209P JC-1, MRSA M126, *Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* GN10362, respectively. Within this series of carbapenem derivatives, the following are also included:



Compound	R1	R2	Formula
267172	O ⁻	6-Me-imidazo[5,1-b] -thiazolium-5-yl-CH ₂ NHCO	C ₂₂ H ₂₇ N ₆ O ₅ S ₂
267173	OH	imidazo[5,1-b]thiazol-3-yl-CH(OH)	C ₂₀ H ₂₄ N ₄ O ₅ S ₂
267174	O ⁻	6-Me-imidazo[5,1-b] -thiazolium-2-yl-CH(OH)	C ₂₁ H ₂₆ N ₄ O ₅ S ₂
267175	O ⁻	6-(NH ₂ COCH ₂)- -imidazo[5,1-b]thiazolium-2-yl-CH ₂	C ₂₂ H ₂₇ N ₆ O ₅ S ₂
267176	OH	(Z)-imidazo[5,1-b]thiazol-3-yl-CH=CH	C ₂₁ H ₂₄ N ₄ O ₄ S ₂
267177	O ⁻	(Z)-6-Me-imidazo[5,1-b]- thiazolium-3-yl-CH=CH	C ₂₂ H ₂₆ N ₄ O ₄ S ₂
267178	O ⁻	6-Me-imidazo[5,1-b]thiazolium-3-yl	C ₂₀ H ₂₄ N ₄ O ₄ S ₂
267179	O ⁻	(E)-6-(NH ₂ COCH ₂)- -imidazo[5,1-b]thiazolium-2-yl-CH=CH	C ₂₃ H ₂₇ N ₆ O ₅ S ₂
267180	O ⁻	(Z)-6-(NH ₂ COCH ₂)- -imidazo[5,1-b]thiazolium-2-yl-CH=CH	C ₂₃ H ₂₇ N ₆ O ₅ S ₂
267181	O ⁻	6-(NH ₂ COCH ₂ CH ₂)- -imidazo[5,1-b]thiazolium-2-yl-CH ₂	C ₂₄ H ₃₁ N ₆ O ₅ S ₂
267182	O ⁻	(Z)-6-(NH ₂ COCH ₂ CH ₂)- -imidazo[5,1-b]thiazolium-3-yl-CH=CH	C ₂₄ H ₂₉ N ₆ O ₅ S ₂
267183	O ⁻	(Z)-6-(NH ₂ COCH ₂ CH ₂)- -imidazo[5,1-b]thiazolium-2-yl-CH=CH	C ₂₄ H ₂₉ N ₆ O ₅ S ₂

SOURCE – Meiji Seika.

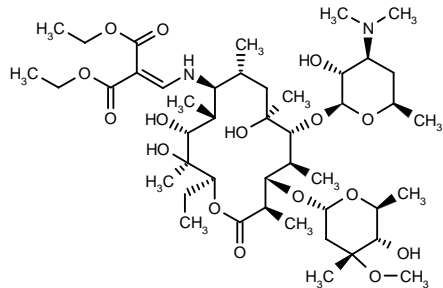
REFERENCES

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WO 9823623.

MISCELLANEOUS ANTIBIOTICS

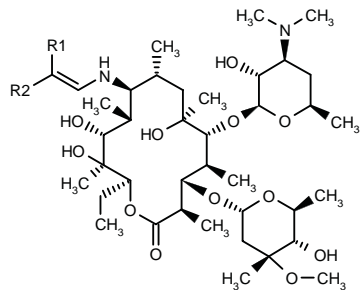
265149

9(S)-[2,2-Bis(ethoxycarbonyl)vinylamino]-9-deoxy-erythromycin A



C45 H80 N2 O16; Mol wt: 905.1250

ACTION – Semisynthetic macrolide antibiotic with *in vitro* antibacterial activity and spectrum similar to erythromycin, reported to be active against Gram-positive microorganisms such as *Streptococcus faecalis* ATCC 8043, *Staphylococcus epidermidis* ATCC 12228 and *Staphylococcus aureus* ATCC 6538. Other compounds from this series of 9-*N*-ethenyl derivatives of 9(S)-erythromcyclamine include the following:



Compound	R1	R2	Formula
265849	CO2Et	CN	C ₄₃ H ₇₃ N ₃ O ₁₄
265850	Ac	Ac	C ₄₃ H ₇₆ N ₂ O ₁₄
265851	CN	CN	C ₄₁ H ₇₀ N ₄ O ₁₂
265852	CO2Et	Ac	C ₄₄ H ₇₈ N ₂ O ₁₅

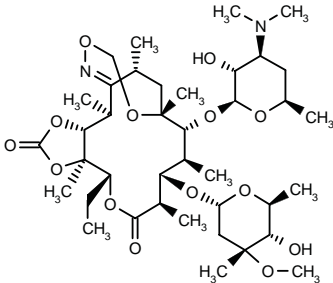
SOURCE – Pliva.

REFERENCES

1. Kujundzic, N. et al. (Pliva Pharmaceutical, Chem., Food & Cosmetic Ind., Inc.) 9-*N*-Ethenyl derivs. of 9(S)-erythromcyclamine. EP 838470, JP 98182689.

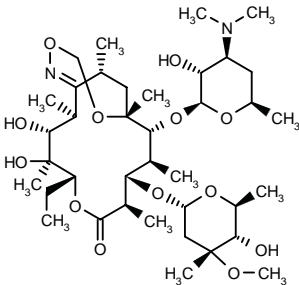
266092

(2*R*,3*R*,7*S*,8*R*,11*R*,12*S*,13*S*,14*S*,15*R*,20*R*)-12-(2,6-Dideoxy-4-*C*,4-*O*-dimethyl- α -L-altropyranosyloxy)-14-[3-(dimethylamino)-3,4,6-trideoxy- β -D-glucopyranosyloxy]-8-ethyl-2,7,11,13,15,20-hexamethyl-4,6,9,16,18-pentaoxa-19-azatricyclo[13,4,2,0^{3,7}]henicosa-1(19)-ene-5,10-dione

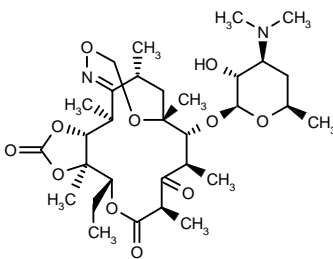


C39 H66 N2 O14; Mol wt: 786.9504

ACTION – Semisynthetic macrolide antibiotic with similar *in vitro* antibacterial activity compared to erythromycin A. Other compounds from this series of 6,9-bridged erythromycin derivatives are:



266136: C38 H68 N2 O13



266137: C31 H50 N2 O11

SOURCE – Abbott.

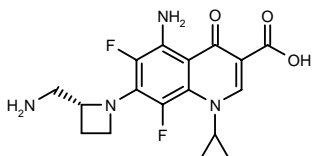
REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) 6,9-Bridged erythromycin derivs. US 5780605.

MISCELLANEOUS ANTIBACTERIAL DRUGS

264578

5-Amino-7-[2(*R*)-(aminomethyl)-1-azetidynyl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C17 H18 F2 N4 O3; Mol wt: 364.3502

M.p. 237-9 °C (*decomp.*), $[\alpha]_D^{23}$ -96.6° (*c* 1.042, 1M NaOH).

ACTION – Quinolone antibacterial agent proven to be more active than sparfloxacin against *Staphylococcus aureus* 209P JC-1 (MIC = 0.0125 µg/ml), *Escherichia coli* NIHJ JC-2 (MIC = 0.003 µg/ml or less) and *Pseudomonas aeruginosa* 12 (MIC = 0.05 µg/ml).

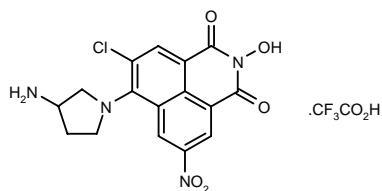
SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Fujita, M. et al. 7-(2-Aminomethyl-1-azetidinyl)-4-oxoquinoline-3-carboxylic acids as potent antibacterial agents: Design, synthesis, and antibacterial activity. *Chem Pharm Bull* 1998, 46(5): 787.

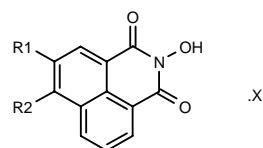
265454

6-(3-Aminopyrrolidin-1-yl)-5-chloro-2-hydroxy-8-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione trifluoroacetate

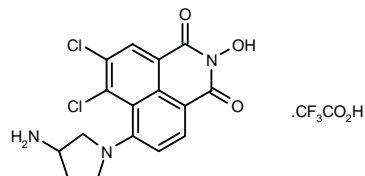


C16 H13 Cl N4 O5 . C2 H F3 O2; Mol wt: 490.7766

ACTION – Antibacterial agent, a selective inhibitor of bacterial DNA gyrase ($IC_{50} = 0.7 \mu M$) and topoisomerase IV ($IC_{50} = 9 \mu M$). Compound exhibited MIC values of 0.5, 0.5, 2.0 and 4.0 $\mu g/ml$, respectively, when tested against *Escherichia coli* B90, *E. coli* TolC, *Bacillus subtilis* RB1 and *Streptococcus pyogenes* C203. Other compounds from this series of benzo[de]isoquinoline-1,3-diones include the following:



Compound	R1	R2	X	Formula
267704	Br	NH2		C ₁₂ H ₇ BrN ₂ O ₃
267705	Cl	3-(NH2CH2)- -1-pyrrolidinyl	HCl	C ₁₇ H ₁₆ ClN ₂ O ₃ .HCl
267706	Cl	3-(NH2CH2)-3-Me- -1-pyrrolidinyl	CF3CO2H	C ₁₈ H ₁₈ ClN ₂ O ₃ .C ₂ H ₃ O ₂



267707: C16 H13 Cl2 N3 O3 . C2 H F3 O2

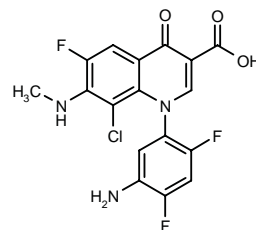
SOURCE – Warner-Lambert.

REFERENCES

1. Amegadzie, A.K. et al. (Warner-Lambert Co.) *Isoquinolones*. WO 9819648.

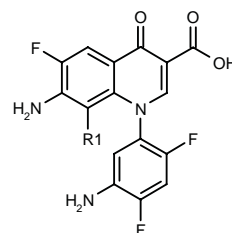
266178

1-(5-Amino-2,4-difluorophenyl)-8-chloro-6-fluoro-7-(meth-
ylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C17 H11 Cl F3 N3 O3: Mol wt: 397.7389

ACTION – Quinolone antibacterial agent with more potent *in vitro* activity against *Staphylococcus aureus* 209P (MIC = 0.013 µg/ml), *Staphylococcus epidermidis* IFO12293 (MIC = 0.025 µg/ml) and *Pseudomonas aeruginosa* IFO3445 (MIC = 0.20 µg/ml) than ciprofloxacin (MIC = 0.10, 0.78 and 0.39 µg/ml, respectively), levofloxacin (MIC = 0.20, 0.39 and 0.78 µg/ml, respectively), sparfloxacin (MIC = 0.05, 0.20 and 0.78 µg/ml, respectively) and tosufloxacin (MIC = 0.05, 0.20 and 0.39 µg/ml, respectively), and reported to possess good oral absorption. Other related compounds include the following:



Compound	R1	Formula
267081	Cl	C ₁₆ H ₉ ClF ₃ N ₃ O ₃
267082	Me	C ₁₇ H ₁₂ F ₃ N ₃ O ₃

SOURCE – Wakunaga.

REFERENCES

1. Sakae, N. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Novel pyridonecarboxylic acid derivs. or salts thereof and drugs containing the same as the active ingredient.* WO 9823592.

EBPH

264896

Human eosinophil-derived basic protein

ACTION – Human eosinophil-derived basic protein (EDBP) derived from IL-5-cultured umbilical cord blood cells, potentially useful for the treatment of parasitic and bacterial infections and cancer. Inhibitors or antagonists of EBPH and antisense sequences to polynucleotides encoding EBPH are also described as useful for eosinophil-associated disorders such as type I allergic reactions.

SOURCE – Incyte.

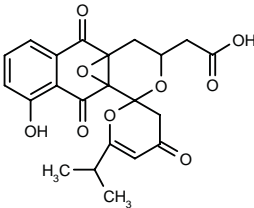
REFERENCES

1. Akerblom, I.E. (Incyte Pharmaceuticals, Inc.) *Human eosinophil-derived basic protein.* WO 9817794.

SPIROXIMICIN

265283

2-[4a,10a-Epoxy-9-hydroxy-6'-isopropyl-4',5,10-trioxo-3,3',4,4',4a,5,10,10a-octahydrospiro[naphtho[2,3-*c*]pyran-1,2'-pyran-3-yl]acetic acid



C22 H20 O9; Mol wt: 428.3910

ACTION – Antibacterial agent isolated from *Amycolatopsis* sp. MJ66-59F3 (FERM P-15801), giving MIC values of 25 µg/ml when tested against *Staphylococcus aureus* FDA 209P, methicillin-resistant *S. aureus* (MRSA) No. 5, MRSA MS-16526, and *Bacillus subtilis* PCI 219.

SOURCE – Microbial Chemistry Research Foundation (JP).

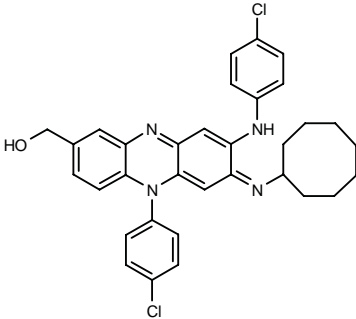
REFERENCES

1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Antibiotic spiroximicin and its preparation method.* JP 98114777.

ANTIMYCOBACTERIAL AGENTS

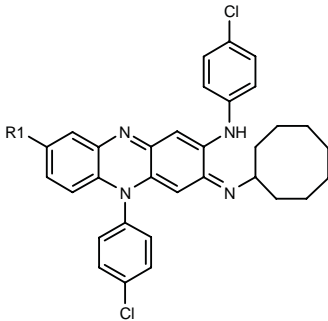
265897

N-(4-Chlorophenyl)-*N*-[5-(4-chlorophenyl)-3-(cyclo-octylimino)-8-(hydroxymethyl)-3,5-dihydrophenazin-2-yl]amine



C33 H32 Cl2 N4 O; Mol wt: 571.5488

ACTION – Antimycobacterial agent active *in vitro* against *Mycobacterium tuberculosis* H37Rv, *Mycobacterium marinum* W2, *Mycobacterium kansasii* NIHJ1619 and *Mycobacterium gordonae* ATCC14470 (MIC = 0.1, 0.05, 0.2 and 0.1 µg/ml, respectively). Other compounds from this series of phenazine derivatives include the following:



Compound	R1	Formula
266568	Me	C ₃₃ H ₃₂ Cl ₂ N ₄
266569	N(Me) ₂	C ₃₄ H ₃₅ Cl ₂ N ₅
266570	CON(Me) ₂	C ₃₅ H ₃₅ Cl ₂ N ₅ O
266571	OMe	C ₃₃ H ₃₂ Cl ₂ N ₄ O

SOURCE – Otsuka.

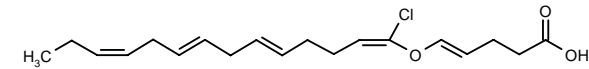
REFERENCES

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MARACENIN D1

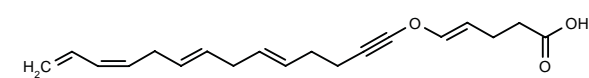
266209

7-Chloro-6-oxa-4(E),7,11(E),14(E),17(Z)-icosapentaenoic acid

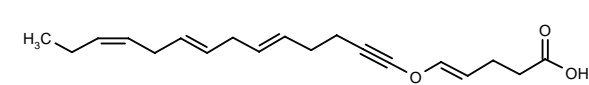


C19 H27 Cl O3; Mol wt: 338.8723

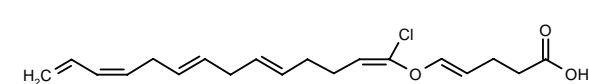
ACTION – Agent for the treatment of tuberculosis isolated from a culture of a strain of *Sorangium cellulosum*. Other compounds isolated from the same source are:



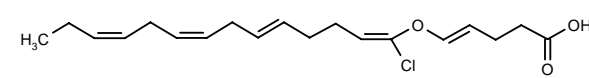
Compound	Isomer	Formula
Maracenin A1 [267287]	14(E)	C ₁₉ H ₂₄ O ₃
Maracenin A2 [267288]	14(Z)	C ₁₉ H ₂₄ O ₃



Compound	Isomer	Formula
Maracenin B1 [267289]	4(E), 14(E)	C ₁₉ H ₂₆ O ₃
Maracenin B2 [267290]	4(E), 14(Z)	C ₁₉ H ₂₆ O ₃
Maracenin B3 [267291]	4(Z), 14(E)	C ₁₉ H ₂₆ O ₃



Compound	Isomer	Formula
Maracenin C1 [267292]	14(E)	C ₁₉ H ₂₅ ClO ₃
Maracenin C2 [267293]	14(Z)	C ₁₉ H ₂₅ ClO ₃



Maracenin D2 [267294]: C19 H27 Cl O3

SOURCE – GBF.

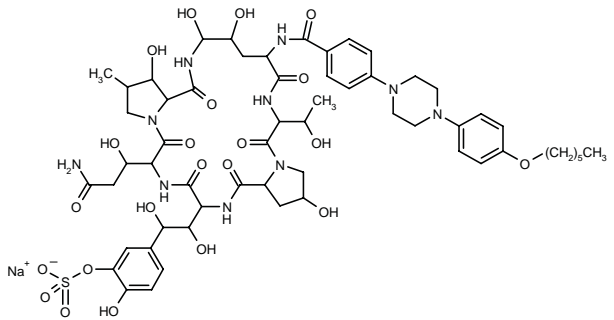
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1. Reichenbach, H. et al. (Gesellschaft für Biotechnologische Forschung mbH) *Unsaturated aliphatic carboxylic acids (maracenines), method for the production thereof and agent against bacteria.* WO 9824751.

ANTIFUNGAL AGENTS

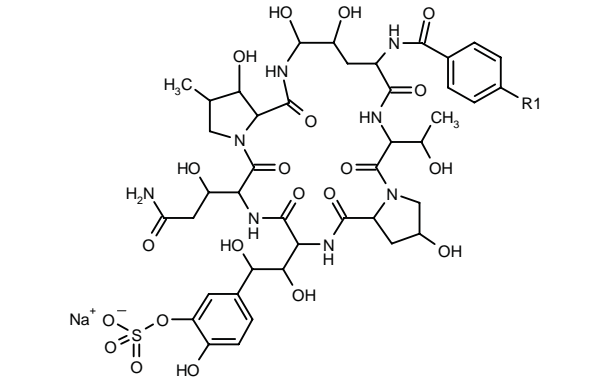
266205

20-(2-Carbamoyl-1-hydroxyethyl)-23-[1,2-dihydroxy-2-(4-hydroxy-3-sulfooxyphenyl)ethyl]-9-[4-[4-(4-hexyloxyphenyl)piperazin-1-yl]benzamido]-2,11,12,15-tetrahydroxy-6-(1-hydroxyethyl)-16-methylperhydrodipyrrolo[2,1-c:2',1'-/][1,4,7,10,13,16]hexaazacycloheneicosine-5,9,14,19,22,25-hexaone sodium salt



C58 H79 N10 Na O22 S; Mol wt: 1323.3660

ACTION – Antifungal agent that acts by inhibiting β -1,3-glucan synthase activity and is also reported to be useful for the treatment of *Pneumocystis carinii* infections. A representative compound from a series of cyclohexapeptides, wherein the following are also included:



Compound	R1	Formula
267232	4-OH-4-[4-(C6H13O)-Ph]-1-Pip	C ₅₉ H ₈₀ N ₉ NaO ₂₃ S
267233	4-[3-(C6H13O)-Ph]-1-Piz	C ₅₈ H ₇₉ N ₁₀ NaO ₂₂ S
267234	5-(4-C5H11-Ph)-1,3,4-thiadiazol-2-yl	C ₅₅ H ₆₉ N ₁₀ NaO ₂₁ S ₂
267235	5-[4-[PhO(CH2)3O]-Ph]-1,3,4-thiadiazol-2-yl	C ₅₉ H ₆₉ N ₁₀ NaO ₂₃ S ₂
267236	5-(4-C5H11O-Ph)-2-thienyl	C ₅₇ H ₇₁ N ₈ NaO ₂₂ S ₂
267237	5-(4-C5H11O-Ph)-2-furyl	C ₅₇ H ₇₁ N ₈ NaO ₂₃ S
267238	4-(C5H11O)-Ph-ethynyl	C ₅₅ H ₆₉ N ₈ NaO ₂₂ S
267239	2-[4-(4-EtO-Ph)-Ph]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl	C ₆₀ H ₆₈ N ₁₁ NaO ₂₂ S ₂
267240	5-(4-C5H11O-Ph)-3-isoxazolyl	C ₅₆ H ₇₀ N ₉ NaO ₂₃ S

SOURCE – Fujisawa.

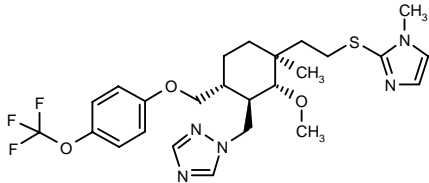
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1. Ohki, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Cyclohexapeptides having antimicrobial activity.* WO 9823637.

RO-09-2474

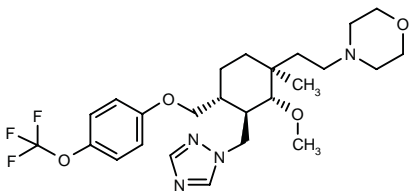
266488

(1*R*,2*R*,3*S*,6*R*)-1-[2-Methoxy-3-methyl-3-[2-(1-methyl-imidazol-2-ylsulfanyl)ethyl]-6-[4-(trifluoromethoxy)-phenoxy]methyl]cyclohexylmethyl]-1*H*-1,2,4-triazole



C25 H32 F3 N5 O3 S; Mol wt: 539.6198

ACTION – Orally active antifungal agent with IC₈₀ values of 0.5, 0.9 and 36 µg/ml against *Candida albicans* CY 3003, *Cryptococcus neoformans* CY 1057 and *Aspergillus fumigatus* CF 1003, respectively, and an ED₅₀ of 50 mg/kg p.o. on day 7 in mice with systemic candidosis; it was about 1/10th as active as fluconazole in this model. Another related compound from this series of cyclohexyl analogs of restricticin is:



Ro-09-2550 [266489]: C25 H35 F3 N4 O4

SOURCE – Nippon Roche.

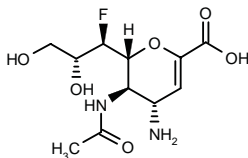
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ANTIVIRAL DRUGS

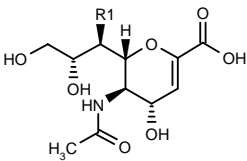
263844

*N*⁵-Acetyl-4-amino-2,4,7-trideoxy-7-fluoro-2,3-didehydro-neuraminic acid



C11 H17 F N2 O6; Mol wt: 292.2613

ACTION – Antiviral agent for the treatment or prevention of influenza virus infections with sialidase (neuraminidase)-inhibitory activity (IC₅₀ = 0.5 µM). Within this series of 2,3-didehydrosialic acid derivatives, the following are also included:



Compound	R1	Formula
267471	OH	C ₁₁ H ₁₇ NO ₈
267472	F	C ₁₁ H ₁₆ FNO ₇

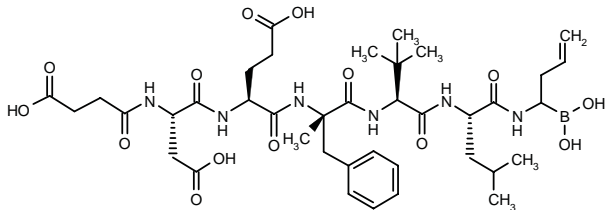
SOURCE – Daikin.

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1. Ohira, Y. (Daikin Industries, Ltd.) *4-Substd.-2,7-dideoxy-7-fluoro-2,3-didehydrosialic acids*. WO 9811083.

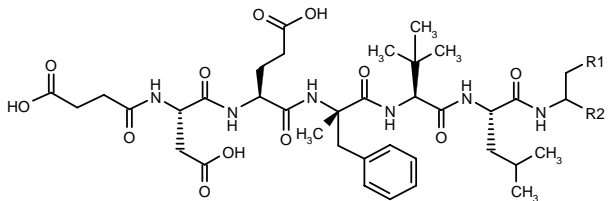
265528

1-[*N*-(4-Hydroxysuccinyl)-*L*-aspartyl-*L*-glutamyl-*L*-(2-methyl)phenylalanyl-*L*-(3-methyl)valyl-*L*-leucylamino]-3-butenylboronic acid



C39 H59 B N6 O14; Mol wt: 846.7341

ACTION – Antiviral agent particularly useful for the treatment of infections caused by hepatitis C and hepatitis G viruses that acts by inhibiting viral proteases such as HCV protease (IC₅₀ = 0.034 mM). Other specifically claimed compounds from this series of peptidic derivatives include the following:



Compound	R1	R2	Formula
266544	vinyl	CHO	C ₄₀ H ₅₈ N ₆ O ₁₃
266545	CF ₂ Me	CHO	C ₄₀ H ₅₆ F ₂ N ₆ O ₁₃
266546	CH ₂ CF ₃	CHO	C ₃₉ H ₅₅ F ₃ N ₆ O ₁₃
266547	Me	B(OH) ₂	C ₃₈ H ₅₆ BN ₆ O ₁₄
266548	Et	B(OH) ₂	C ₃₉ H ₆₁ BN ₆ O ₁₄

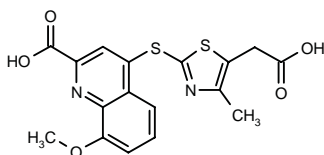
SOURCE – Roche.

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1. Attwood, M.R. et al. (F. Hoffmann-La Roche AG) *Antiviral peptide derivs*. WO 9822496.

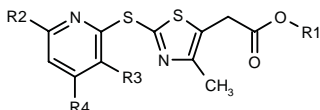
267373

4-[5-(Carboxymethyl)-4-methylthiazol-2-ylsulfany]-8-methoxyquinoline-2-carboxylic acid



C17 H14 N2 O5 S2; Mol wt: 390.4386

ACTION – Antiviral agent structurally related to tiprotimod that acts by increasing cytotoxic T-cell function. Other specifically claimed compounds from this series of thiazole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
267374	Et	H	CO2H	Me	C ₁₅ H ₁₆ N ₂ O ₄ S ₂
267375	H	CO2Et	H	H	C ₁₄ H ₁₄ N ₂ O ₄ S ₂

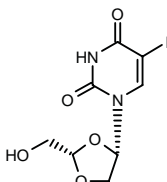
SOURCE – Pfizer.

REFERENCES

1. Kleinman, E.F. et al. (Pfizer Inc.) *Antiviral thiazoles*. US 5789408, WO 9505378.

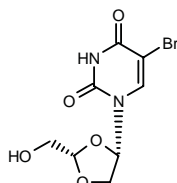
267445

(2*S*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-iodouracil



C8 H9 I N2 O5; Mol wt: 340.0681

ACTION – Antiviral agent for the treatment of Epstein-Barr virus (EBV) infection that exhibits potent inhibition of the replication of EBV ($EC_{50} = 0.1 \mu M$) and very low cytotoxicity. Compound is selective for EBV, showing little activity against other viruses such as herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), cytomegalovirus (CMV), hepatitis B virus (HBV) and HIV. Another compound from this series of β -L-dioxolane nucleoside analogs is:



267446: C8 H9 Br N2 O5

SOURCES – University of Georgia Research Foundation, Athens, GA (US); Yale University, New Haven, CT (US).

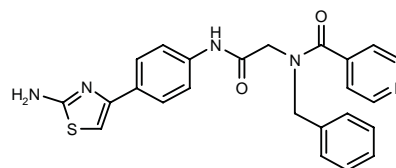
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1. Chu, C.K. et al. (Yale University;University of Georgia) *L-β-Dioxolane uridine analog administration for treating Epstein-Barr virus infection*. US 5792773.

BILS-45-BS

263560

N-[2-[4-(2-Amino-4-thiazolyl)phenylamino]-2-oxoethyl]-*N*-(benzyl)pyridine-4-carboxamide



C24 H21 N5 O2 S; Mol wt: 443.5289

ACTION – Antiviral agent, an inhibitor of herpes simplex virus type 1 (HSV-1) helicase–primase proven to inhibit the helicase, primase and DNA-dependent ATPase activities of the enzyme with IC_{50} values of 0.9, 0.3 and 0.11 μM , respectively. It was more potent than aciclovir against wild-type HSV-1 and HSV-2 strains, as well as aciclovir-resistant HSV isolates (EC_{50} approx. 0.15 μM). Compound was orally active against both HSV-1 and HSV-2 infections in experimental animal models; in a nude mouse model of aciclovir-resistant HSV-1 infection due to *dl*sptk and PAA'5 mutants, the ED_{50} was 55 and 63 mg/kg/day p.o., respectively, whereas oral aciclovir (100 or 125 mg/kg/day t.i.d.) had no effect. The oral bioavailability in mice was 49%.

SOURCE – Boehringer Ingelheim.

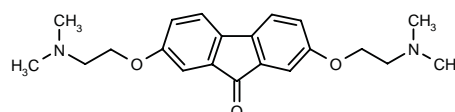
REFERENCES

1. Boehringer Ingelheim Pharmaceuticals, Inc.; Boehringer Ingelheim (Canada) Ltd. *Phenyl thiazole derivs. with anti herpes virus properties*. EP 871619, WO 9724343.
2. Duan, J. et al. *A HSV helicase-primase inhibitor, BILS 45 BS, with potent oral activity against acyclovir-resistant infection in nude mice*. Antivir Res 1998, 37(3): Abstr 132.
3. Luzzi, M. et al. *Aminothiazolyl-phenyl-based inhibitors of HSV helicase-primase: A novel class of orally active antiherpetic agents*. Antivir Res 1998, 37(3): Abstr 11.
4. Simoneau, B. et al. *Helicase-primase inhibitors as novel anti-HSV agents*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abstr MEDI 212.

VIR-112

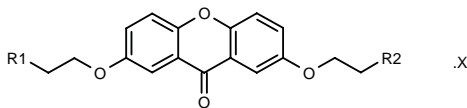
264348

2,7-Bis[2-(dimethylamino)ethoxy]fluoren-9-one

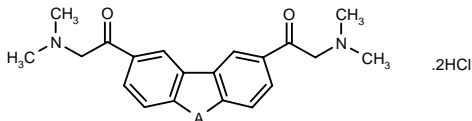


C21 H26 N2 O3; Mol wt: 354.4474

ACTION – Antiviral agent for the treatment or prevention of hepatitis C viral infections, a representative compound from a series of tricyclic derivatives, wherein the following are also included:



Compound	R1=R2	X	Formula
RES-099 [267360]	CH2N(Me)2		C ₂₃ H ₃₀ N ₂ O ₄
RES-162 [267361]	NH2		C ₁₇ H ₁₈ N ₂ O ₄
VIR-069 [267362]	N(Me)2	2HCl	C ₂₁ H ₂₆ N ₂ O ₄ ·2HCl



Compound	A	Formula
VIR-071 [267363]	S	C ₂₀ H ₂₂ N ₂ O ₂ S·2HCl
VIR-072 [267364]	O	C ₂₀ H ₂₂ N ₂ O ₃ ·2HCl

SOURCE – Eisai.

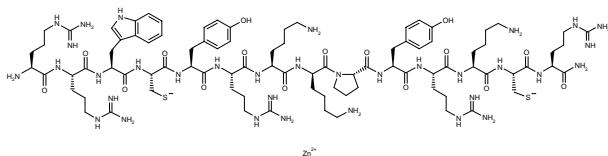
REFERENCES

1. Kai, Y. et al. (Eisai Co., Ltd.) *Preventive and therapeutic agents for viral infection*. JP 98101591.

AIDS MEDICINES

264857

Arginyl-arginyl-tryptophanyl-cysteinyl-tyrosyl-arginyl-lysyl-D-lysyl-prolyl-tyrosyl-arginyl-lysyl-cysteinyl-argininamide zinc salt



C88 H142 N34 O16 S2 Zn; Mol wt: 2061.8340

ACTION – Antiviral agent for AIDS with potent anti-HIV activity in infected MT-4 cells (IC₅₀ = 0.014 µg/ml) and low cytotoxicity in uninfected cells (CC₅₀ = 54.63 µg/ml; selectivity index = 4052). A representative compound from a series of novel transition metal salts of polypeptides with improved anti-HIV activity.

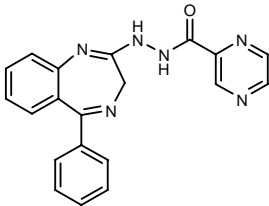
SOURCE – Seikagaku.

REFERENCES

1. Matsumoto, A. and Waki, M. (Seikagaku Corp.) *Polypeptide transition metal salts and method of enhancing anti-HIV activity of polypeptide*. WO 9816555.

265085

N²-(5-Phenyl-3*H*-1,4-benzodiazepin-2-yl)pyrazine-2-carbohydrazide



C20 H16 N6 O; Mol wt: 356.3874

ACTION – Antiviral agent for AIDS that acts by selectively inhibiting HIV integrase. Activity was demonstrated in several *in vitro* tests, by inhibition of HIV integrase substrate cleavage (IC₅₀ = 2 µM), inhibition of strand transfer by HIV integrase (IC₅₀ = 2-3 µM) and inhibition of assembly of HIV-1 integrase (IC₅₀ = 5 µM).

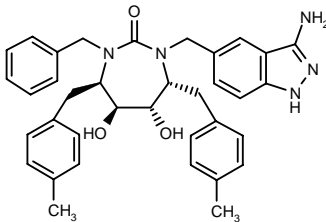
SOURCE – Merck & Co.

REFERENCES

1. Bell, I.M. et al. (Merck & Co., Inc.) *Benzodiazepine hydrazide derivs. as inhibitors of HIV integrase*. WO 9818473.

265470

[4*R*-(4α,5α,6β,7β)]-1-(3-Aminoindazol-5-ylmethyl)-3-benzyl-5,6-dihydroxy-4,7-bis(4-methylbenzyl)perhydro-1,3-diazepin-2-one



C36 H39 N5 O3; Mol wt: 589.7361

ACTION – Antiviral agent for AIDS, a specific inhibitor of HIV protease.

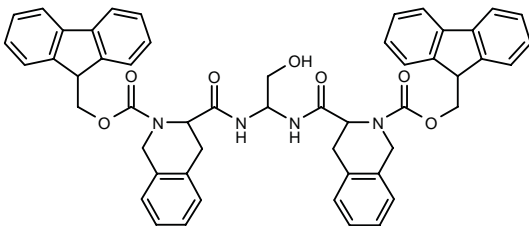
SOURCE – DuPont Pharm.

REFERENCES

1. Rodgers, J.D. and Kaltenbach, R.F. III (The Du Pont Merck Pharmaceutical Co.) *1-(3-Aminoindazol-5-yl)-3-phenylmethyl-cyclic ureas useful as HIV protease inhibitors*. WO 982008.

265970

N,N'-Bis[2-(fluorenyl-9-ylmethoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl]-2,2-(diamino)ethanol



C52 H46 N4 O7; Mol wt: 838.9564

M.p. 199-202 °C, [α]_D²¹ −3.5° (c 1.0, MeOH).

ACTION – Anti-HIV-1 pseudotriptide containing the *gem*-diaminoserine core structure, with potent inhibitory activity against HIV-1 protease (IC_{50} = 385 nmol/l against purified recombinant enzyme).

SOURCE – University of Ferrara, Ferrara (IT).

REFERENCES

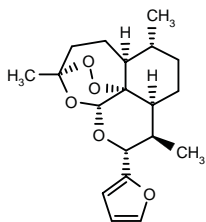
1. Marastoni, M. et al. *Structure-activity relationships of HIV-1 protease inhibitors containing gem-diaminoserine core unit*. *Arzneim-Forsch Drug Res* 1998, 48(6): 709.

TREATMENT OF PROTOZOAL DISEASES

MHP-46

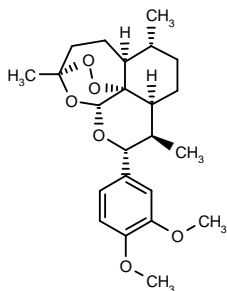
267142

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*S*,12*aR*)-Octahydro-3,6,9-trimethyl-10-(2-furyl)-3,12-epoxy-12*H*-pyrano[4,3-*j*]-[1,2]benzodioxepin



C₁₉ H₂₆ O₅; Mol wt: 334.4094

ACTION – Potent antimalarial agent (IC_{50} = 1.4 nM) from a series of trioxanes related to artemisinin (qinghaosu), wherein the following is also included:



MHP-43 [267154]: C₂₃ H₃₂ O₆

SOURCE – Johns Hopkins University, Baltimore, MD (US).

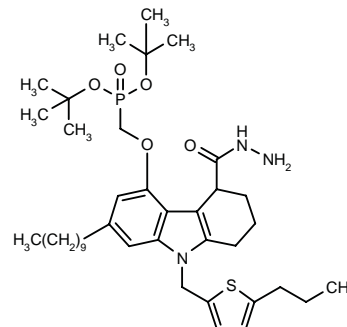
REFERENCES

1. Posner, G.H. *Malaria chemotherapy: New antimalarial trioxanes related to natural artemisinin (qinghaosu)*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 223.

TREATMENT OF SEPTIC SHOCK

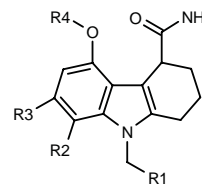
265076

5-(Di-*tert*-butoxyphosphoryl-methoxy)-7-decyl-9-(5-propylthien-2-ylmethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide



C₄₀ H₆₄ N₃ O₅ P S; Mol wt: 730.0016

ACTION – Agent for the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis, an inhibitor of secretory phospholipase A₂ (sPLA₂). Within this series of tricyclic derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
267741	H	H	(CH ₂) ₅ CN	H	C ₂₀ H ₂₅ N ₃ O ₂
267742	3,5-(Pr) ₂ -Ph	(CH ₂) ₅ -CONH ₂	H	CH ₂ CO ₂ Et	C ₃₆ H ₄₉ N ₃ O ₅
267743	cyclopentyl	H	H	CH ₂ CO ₂ Pr	C ₂₄ H ₃₂ N ₂ O ₄

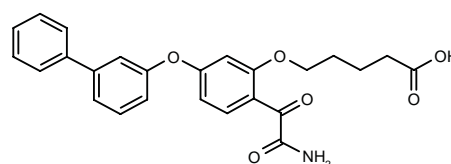
SOURCE – Lilly.

REFERENCES

1. Back, N.J. et al. (Eli Lilly and Company) *Subst. tricyclics*. WO 9818464.

266229

5-[2-(2-Amino-2-oxoacetyl)-5-(3-biphenyloxy)-phenoxy]pentanoic acid



C₂₅ H₂₃ N O₆; Mol wt: 433.4577

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

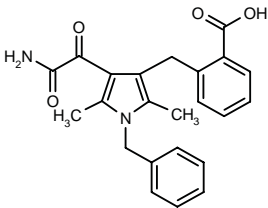
SOURCE – Lilly.

REFERENCES

1. Goodson, T. Jr. et al. (Eli Lilly and Company) *Phenyl glyoxamides as sPLA₂ inhibitors*. WO 9824794.

267634

2-[4-(2-Amino-2-oxoacetyl)-1-benzyl-2,5-dimethylpyrrol-3-ylmethyl]benzoic acid



C23 H22 N2 O4; Mol wt: 390.4368

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

SOURCE – Lilly.

REFERENCES

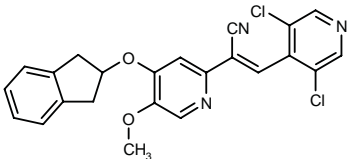
1. Bach, N.J. et al. (Eli Lilly and Company) *Pyrroles as sPLA2 inhibitors*. WO 9825609.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

264385

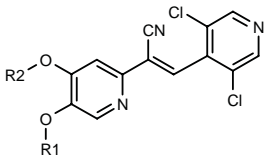
3-(3,5-Dichloropyridin-4-yl)-2-[4-(indan-2-yloxy)-5-methoxypyridin-2-yl]-2-propenenitrile



C23 H17 Cl2 N3 O2; Mol wt: 438.3123

ACTION – Agent for the treatment of inflammatory and autoimmune diseases, a selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.65 nM vs. > 100 μM for PDE3 and PDE5) with additional inhibitory activity against the production of tumor necrosis factor

(TNF-α; IC₅₀ = 2.9 μM). Within this series of vinylpyridines, the following compounds are also included:



Compound	R1	R2	Formula
267489	Me	cyclopentyl	C ₁₉ H ₁₇ Cl ₂ N ₃ O ₂
267490	Me	CH2CH2Ph	C ₂₂ H ₁₇ Cl ₂ N ₃ O ₂
267491	Me	(CH2)3Ph	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₂
267492	Me	Bu	C ₁₈ H ₁₇ Cl ₂ N ₃ O ₂
267493	Me	CH(Et)2	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₂
267494	Et	cyclopentyl	C ₂₀ H ₁₉ Cl ₂ N ₃ O ₂
267495	Me	3-THF	C ₁₈ H ₁₅ Cl ₂ N ₃ O ₃

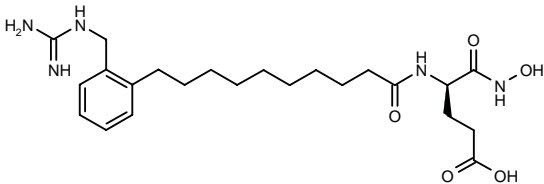
SOURCE – SS Pharmaceutical.

REFERENCES

1. Yamazaki, K. et al. (SS Pharmaceutical, Ltd.) *Substd. vinylpyridine derivs. and drugs containing the same*. EP 882714, WO 9813348.

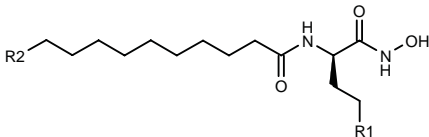
264426

N-[10-[2-(Guanidinomethyl)phenyl]decanoyl]-D-glutamic acid hydroxyamide



C23 H37 N5 O5; Mol wt: 463.5753

ACTION – Agent for the treatment of disorders involving tissue degradation such as rheumatoid arthritis that acts by inhibiting matrix metalloproteinases (MMPs) such as gelatinase A (MMP-3; IC₅₀ = 0.004 μM) and collagenase 3 (MMP-13; IC₅₀ = 0.004 μM). Within this series of hydroxamic acid derivatives, the following are also included:



Compound	R1	R2	Formula
267481	CH2CH2NH2	2-[NH2C(=NH)NHCH2]-Ph	C ₂₄ H ₄₂ N ₆ O ₃
267482	CO2H	2-(NH2CH2)-Ph	C ₂₂ H ₃₅ N ₃ O ₅
267483	CH2CH2NH2	2-(NH2CH2)-Ph	C ₂₃ H ₄₀ N ₄ O ₃
267484	CO2H	Ph	C ₂₁ H ₃₂ N ₂ O ₅
267485	CO2H	CH2Ph	C ₂₂ H ₃₄ N ₂ O ₅
267486	CO2H	3-(CO2Me)-Ph	C ₂₃ H ₃₄ N ₂ O ₇
267487	CO2H	CH2CH2Ph	C ₂₃ H ₃₆ N ₂ O ₅
267488	CO2H	(CH2)3Ph	C ₂₄ H ₃₈ N ₂ O ₅

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

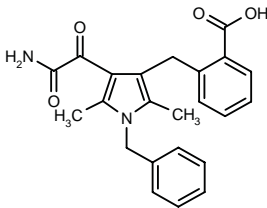
SOURCE – Lilly.

REFERENCES

1. Goodson, T. Jr. et al. (Eli Lilly and Company) *Phenyl glyoxamides as sPLA₂ inhibitors*. WO 9824794.

267634

2-[4-(2-Amino-2-oxoacetyl)-1-benzyl-2,5-dimethylpyrrol-3-ylmethyl]benzoic acid



C23 H22 N2 O4; Mol wt: 390.4368

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂) with potential in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

SOURCE – Lilly.

REFERENCES

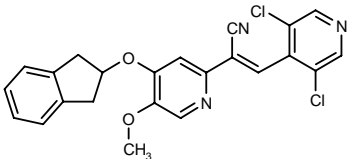
1. Bach, N.J. et al. (Eli Lilly and Company) *Pyrroles as sPLA2 inhibitors*. WO 9825609.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

264385

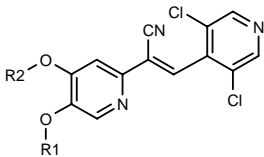
3-(3,5-Dichloropyridin-4-yl)-2-[4-(indan-2-yloxy)-5-methoxypyridin-2-yl]-2-propenenitrile



C23 H17 Cl2 N3 O2; Mol wt: 438.3123

ACTION – Agent for the treatment of inflammatory and autoimmune diseases, a selective inhibitor of phosphodiesterase type 4 (PDE4; IC₅₀ = 0.65 nM vs. > 100 μM for PDE3 and PDE5) with additional inhibitory activity against the production of tumor necrosis factor

(TNF-α; IC₅₀ = 2.9 μM). Within this series of vinylpyridines, the following compounds are also included:



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267491	Me	(CH2)3Ph	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₂
267492	Me	Bu	C ₁₈ H ₁₇ Cl ₂ N ₃ O ₂
267493	Me	CH(Et)2	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₂
267494	Et	cyclopentyl	C ₂₀ H ₁₉ Cl ₂ N ₃ O ₂
267495	Me	3-THF	C ₁₈ H ₁₅ Cl ₂ N ₃ O ₃

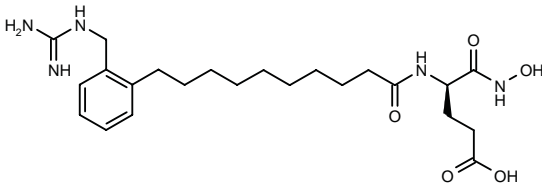
SOURCE – SS Pharmaceutical.

REFERENCES

1. Yamazaki, K. et al. (SS Pharmaceutical, Ltd.) *Substd. vinylpyridine derivs. and drugs containing the same*. EP 882714, WO 9813348.

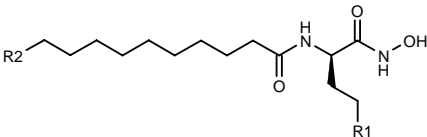
264426

N-[10-[2-(Guanidinomethyl)phenyl]decanoyl]-D-glutamic acid hydroxyamide



C23 H37 N5 O5; Mol wt: 463.5753

ACTION – Agent for the treatment of disorders involving tissue degradation such as rheumatoid arthritis that acts by inhibiting matrix metalloproteinases (MMPs) such as gelatinase A (MMP-3; IC₅₀ = 0.004 μM) and collagenase 3 (MMP-13; IC₅₀ = 0.004 μM). Within this series of hydroxamic acid derivatives, the following are also included:



Compound	R1	R2	Formula
267481	CH2CH2NH2	2-[NH2C(=NH)NHCH2]-Ph	C ₂₄ H ₄₂ N ₆ O ₃
267482	CO2H	2-(NH2CH2)-Ph	C ₂₂ H ₃₅ N ₃ O ₅
267483	CH2CH2NH2	2-(NH2CH2)-Ph	C ₂₃ H ₄₀ N ₄ O ₃
267484	CO2H	Ph	C ₂₁ H ₃₂ N ₂ O ₅
267485	CO2H	CH2Ph	C ₂₂ H ₃₄ N ₂ O ₅
267486	CO2H	3-(CO2Me)-Ph	C ₂₃ H ₃₄ N ₂ O ₇
267487	CO2H	CH2CH2Ph	C ₂₃ H ₃₆ N ₂ O ₅
267488	CO2H	(CH2)3Ph	C ₂₄ H ₃₈ N ₂ O ₅

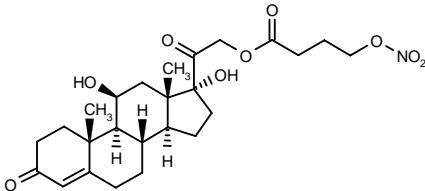
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Samizo, F. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Hydroxamic acids*. WO 9815525.

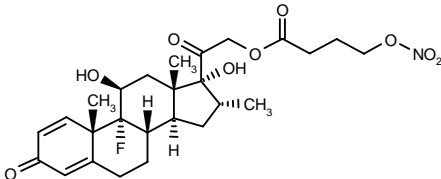
264442

11β,17α-Dihydroxy-21-[4-(nitrooxy)butyryloxy]pregn-4-ene-3,20-dione



C25 H35 N O9; Mol wt: 493.5495

ACTION – Nitrate ester of hydrocortisone with comparable potency to parent compound in the adjuvant-induced arthritis model in rats, producing 45% inhibition at 5 mg/kg i.p. vs. 40% inhibition for hydrocortisone at the same dose, while exhibiting greatly improved gastric tolerability. No toxicity was observed following administration of 50 mg/kg p.o. to mice. Another compound from this series of nitrate esters of corticoids is:



267698: C26 H34 F N O9

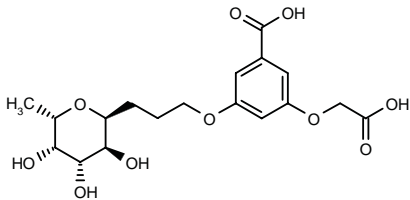
SOURCE – NicOx.

REFERENCES

1. Del Soldato, P. (NicOx SA) *Nitrate esters of corticoid cpds. and pharmaceutical applications thereof*. WO 9815568.

266201

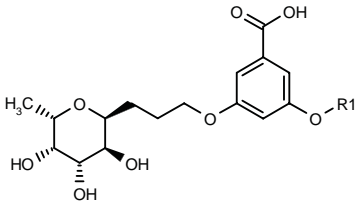
3-(Carboxymethoxy)-5-[3-(α-L-galactopyranosyl)propoxy]-benzoic acid



C18 H24 O10; Mol wt: 400.3776

ACTION – Agent for the treatment of autoimmune diseases such as rheumatoid arthritis and insulin-dependent diabetes mellitus (IDDM), transplant rejection, adult respiratory distress syndrome (ADRS), inflammatory and allergic skin disorders such as psoriasis, cardiovascular disorders, septic shock and cancer, an antagonist of E- and P-selectins shown to inhibit leukocyte

adhesion *in vivo* in rats (43% inhibition at 3 mg/kg i.v.). Within this series of benzoic acid derivatives, the following are also included:



Compound	R1	Formula
267302	4-CO2H-1-Pip-CO	C ₂₃ H ₃₁ NO ₁₁
267303	CH(CO2H)2	C ₁₉ H ₂₄ O ₁₂

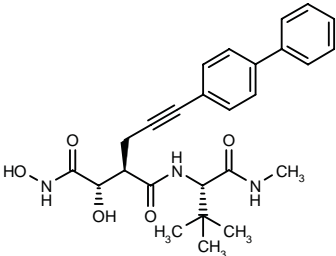
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Kretschmar, G. and Toepfer, A. (Hoechst Research & Technology Deutschland GmbH & Co. KG) *Antiadhesive benzoic acid derivs*. WO 9823626.

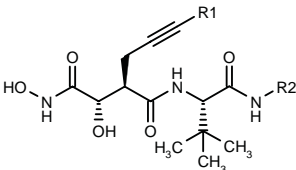
266210

2(*R*)-[3-(4-Biphenyl)-2-propynyl]-*N*¹-[2,2-dimethyl-1(*S*)-(*N*-methylcarbamoyl)propyl]-3(*S*),*N*⁴-dihydroxysuccinamide

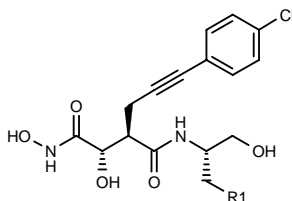


C26 H31 N3 O5; Mol wt: 465.5469

ACTION – Agent for the treatment of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, tumor invasion by secondary metastases and multiple sclerosis, an inhibitor of matrix metalloproteinases. Other specifically claimed compounds from this series of succinamide derivatives include the following:



Compound	R1	R2	Formula
267295	4-CF3-Ph	Me	C ₂₁ H ₂₆ F ₃ N ₃ O ₅
267296	4-Cl-Ph	Me	C ₂₀ H ₂₆ ClN ₃ O ₅
267297	4-(MeOCH2CH2O)-Ph	Me	C ₂₃ H ₃₃ N ₃ O ₇
267300	2-thienyl	2-Pyr	C ₂₂ H ₂₆ N ₄ O ₅ S



Compound	R1	Formula
267298	Ph	C ₂₂ H ₂₃ ClN ₂ O ₅
267299	5-imidazolyl	C ₁₉ H ₂₁ ClN ₄ O ₅

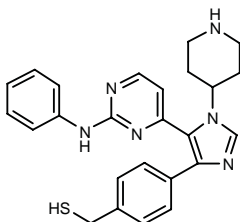
SOURCE – British Biotech.

REFERENCES

- Whittaker, M. et al. (British Biotech plc) *Metalloproteinase inhibitors*. WO 9824759.

267647

N-Phenyl-*N*-[4-[1-(4-piperidyl)-4-[4-(sulfanylmethyl)-phenyl]imidazol-5-yl]pyrimidin-2-yl]amine



C₂₅ H₂₆ N₆ S; Mol wt: 442.5884

ACTION – An inhibitor of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF), as well as CSBP/p38/RK kinase activity. Potentially useful in the treatment of a broad range of conditions including rheumatoid arthritis, osteoarthritis, septic shock, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, Alzheimer's disease, psoriasis, restenosis, osteoporosis, graft-versus-host disease, transplant rejection and ulcerative colitis.

SOURCE – SmithKline Beecham.

REFERENCES

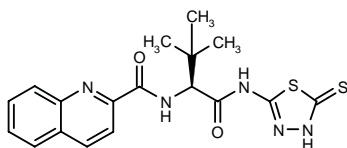
- Adams, J.L. et al. (SmithKline Beecham Corp.) *Novel cpds*. WO 9825619.

PS-508

266868

N-[2,2-Dimethyl-1(*S*)-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylcarboxamido)propyl]quinoline-2-carboxamide

N-(2-Quinolylcarbonyl)-*L*-*tert*-valine (5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylcarbonyl)amide



C₁₈ H₁₉ N₅ O₂ S₂; Mol wt: 401.5131

ACTION – Nonhydroxamic acid inhibitor of matrix metalloproteinases (MMPs) with potent and selective activity against MMP-3 (stromelysin; IC₅₀ = 0.04 μM). Potentially useful in the treatment of arthritis, inflammatory bowel disease and periodontal disease, among other disorders.

SOURCE – ProScript.

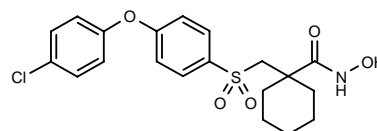
REFERENCES

- Behnke, M.L. et al. *Structure-activity relationship studies of a new non-hydroxamic acid class of inhibitors of MMP-3*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 003.
- Chen, S. et al. *Synthesis of a new non-hydroxamic acid class of inhibitors of MMP-3*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 043.

RS-130830

256579

1-[4-(4-Chlorophenoxy)phenylsulfonylethyl]cyclohexane-1-carboxylic acid



C₂₀ H₂₂ Cl N O₅ S; Mol wt: 423.9148

ACTION – Antiarthritic agent, a metalloprotease inhibitor with high potency and selectivity for collagenase 3 (K_i = 0.52 nM) compared to collagenase 1 (K_i = 590 nM) and good activity against gelatinase A and B (K_i = 0.22 and 0.55 nM, respectively) and stromelysin (K_i = 9.3 nM). RS-130830 inhibited IL-1α-induced hydroxyproline release from bovine nasal cartilage (IC₅₀ = 27 nM) and bovine articular cartilage (IC₅₀ = 200 nM) at concentrations well below the K_i for collagenase 1, indicating that it may inhibit cartilage destruction in human arthritis. In the rabbit partial medial meniscectomy model of osteoarthritis, doses of 3 and 10 mg/kg/day by gavage starting 6 weeks after surgery were able to prevent cartilage damage at blood levels inhibiting collagenase 3 but not collagenase 1.

SOURCE – Roche Bioscience.

REFERENCES

- Atley, L. et al. *RS-130830, a selective inhibitor of collagenase-3 blocks the release of hydroxyproline and a metalloproteinase specific neopeptide, col II CTx, from bovine cartilage exposed to IL-1α*. Arthritis Rheum 1997, 40(9, Suppl.): Abst 584.
- Campbell, J.A. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 004.
- Lollini, L. et al. *Disease modification by RS-130830, a collagenase-3 selective inhibitor, in experimental osteoarthritis*. Arthritis Rheum 1997, 40(9, Suppl.): Abst 341.

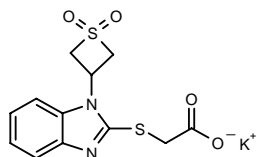
IMMUNOMODULATING AGENTS

THIETHAZOLE

266342

2-[1-(1,1-Dioxothietan-3-yl)-1*H*-benzimidazol-2-ylsulfanyl]acetic acid potassium salt

K-134



C12 H11 K N2 O4 S2; Mol wt: 350.4589

ACTION – Immunomodulating agent and antioxidant, a benzimidazole with broad-spectrum activity. For example, it protected mice from endotoxin-induced lethality, reduced tumor growth in mice bearing sarcoma S180 and melanoma B16, prevented the development of hemolytic anemia in mice, prolonged skin allograft survival in CBA mice receiving allografts from C57BL/6 mice, and enhanced macrophage activity in mice. Depending on the dose or time of administration, the compound suppressed or enhanced DNFB-induced contact hypersensitivity and sheep red blood cell-induced humoral immune responses in mice.

SOURCES – Bashkir Medical University, Ufa (RU); Russian Eye and Plastic Surgery Center, Ufa (RU).

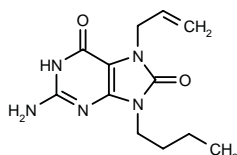
REFERENCES

1. Sadykov, R.F. et al. *Thiethazole as a new immunomodulator*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.28.

267227

7-Allyl-9-butylguanin-8(7*H*)-one

7-Allyl-2-amino-9-butyl-6,7,8,9-tetrahydro-1*H*-purine-6,8-dione



C12 H17 N5 O2; Mol wt: 263.2993

ACTION – Immunostimulant found to potentiate the primary antibody response to sheep erythrocytes in murine spleen and thymus preparations, producing a maximal response about 77-168% that of loxoribine at 2-16 μ M. It was less effective in inducing NK cell activation (21-43% at 4-7 μ M) and mitogenesis in murine spleen cells (36-40% at 11-18 μ M).

SOURCE – Scripps Research Institute, La Jolla, CA (US).

REFERENCES

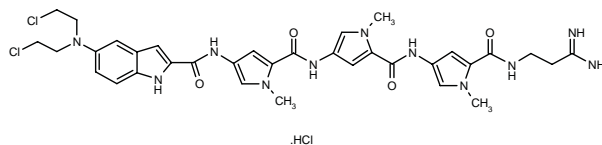
1. Reitz, A. et al. (Scripps Research Institute) *N9 alkyl or aralkyl derivs. of 7,8-disubst. guanines*. US 5786359.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

265489

3-[4-[4-[5-[*N,N*-Bis(2-chloroethyl)amino]-1-methylindol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]propionamide hydrochloride



C34 H39 Cl2 N11 O4 . HCl; Mol wt: 773.1220

ACTION – Antineoplastic and antiviral agent, an alkylating agent structurally related to distamycin A.

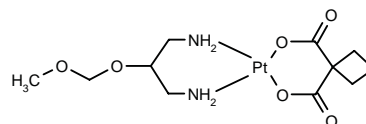
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Benzoheterocyclic distamycin derivs., process for preparing them, and their use as antitumor and antiviral agents*. WO 9821202.

265925

(Cyclobutane-1,1-dicarboxylato)[2-(methoxymethoxy)-propane-1,3-diamine-*N,N'*]platinum(II)



C11 H20 N2 O6 Pt; Mol wt: 471.3670

ACTION – Antineoplastic platinum complex shown to increase survival in mice bearing murine leukemia L1210 (ILSmax = 64.4% at 128 mg/kg/day i.p. x 5 days; ILSmaxcarboplatin = 49.4% at 64 mg/kg/day i.p. x 5 days); LD₅₀ > 200.0 mg/kg vs. 200.0 mg/kg for carboplatin. Other compounds from this series of diamine platinum complexes include the following:

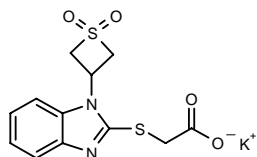
IMMUNOMODULATING AGENTS

THIETHAZOLE

266342

2-[1-(1,1-Dioxothietan-3-yl)-1*H*-benzimidazol-2-ylsulfanyl]acetic acid potassium salt

K-134



C12 H11 K N2 O4 S2; Mol wt: 350.4589

ACTION – Immunomodulating agent and antioxidant, a benzimidazole with broad-spectrum activity. For example, it protected mice from endotoxin-induced lethality, reduced tumor growth in mice bearing sarcoma S180 and melanoma B16, prevented the development of hemolytic anemia in mice, prolonged skin allograft survival in CBA mice receiving allografts from C57BL/6 mice, and enhanced macrophage activity in mice. Depending on the dose or time of administration, the compound suppressed or enhanced DNFB-induced contact hypersensitivity and sheep red blood cell-induced humoral immune responses in mice.

SOURCES – Bashkir Medical University, Ufa (RU); Russian Eye and Plastic Surgery Center, Ufa (RU).

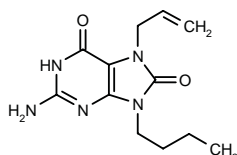
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267227

7-Allyl-9-butylguanin-8(7*H*)-one

7-Allyl-2-amino-9-butyl-6,7,8,9-tetrahydro-1*H*-purine-6,8-dione



C12 H17 N5 O2; Mol wt: 263.2993

ACTION – Immunostimulant found to potentiate the primary antibody response to sheep erythrocytes in murine spleen and thymus preparations, producing a maximal response about 77-168% that of loxoribine at 2-16 μ M. It was less effective in inducing NK cell activation (21-43% at 4-7 μ M) and mitogenesis in murine spleen cells (36-40% at 11-18 μ M).

SOURCE – Scripps Research Institute, La Jolla, CA (US).

REFERENCES

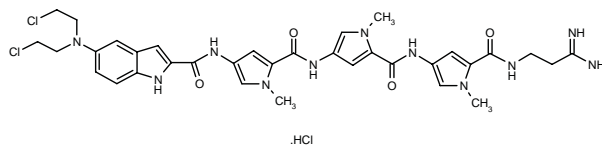
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ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

265489

3-[4-[4-[5-[*N,N*-Bis(2-chloroethyl)amino]-1-methylindol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]-1-methylpyrrol-2-ylcarboxamido]propionamide hydrochloride



C34 H39 Cl2 N11 O4 . HCl; Mol wt: 773.1220

ACTION – Antineoplastic and antiviral agent, an alkylating agent structurally related to distamycin A.

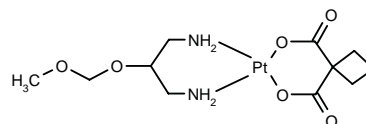
SOURCE – Pharmacia & Upjohn.

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1. Cozzi, P. et al. (Pharmacia & Upjohn SpA) *Benzoheterocyclic distamycin derivs., process for preparing them, and their use as antitumor and antiviral agents*. WO 9821202.

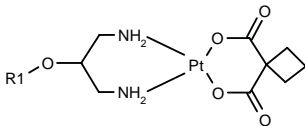
265925

(Cyclobutane-1,1-dicarboxylato)[2-(methoxymethoxy)-propane-1,3-diamine-*N,N'*]platinum(II)



C11 H20 N2 O6 Pt; Mol wt: 471.3670

ACTION – Antineoplastic platinum complex shown to increase survival in mice bearing murine leukemia L1210 (ILSmax = 64.4% at 128 mg/kg/day i.p. x 5 days; ILSmaxcarboplatin = 49.4% at 64 mg/kg/day i.p. x 5 days); LD₅₀ > 200.0 mg/kg vs. 200.0 mg/kg for carboplatin. Other compounds from this series of diamine platinum complexes include the following:



Compound	R1	Formula
266534	Me	C ₁₀ H ₁₈ N ₂ O ₅ Pt
266535	Et	C ₁₁ H ₂₀ N ₂ O ₅ Pt
266536	COBu	C ₁₄ H ₂₄ N ₂ O ₆ Pt
266537	t-BuCO	C ₁₄ H ₂₄ N ₂ O ₆ Pt
266538	COPh	C ₁₆ H ₂₀ N ₂ O ₆ Pt
266539	4-OH-PhCO	C ₁₆ H ₂₀ N ₂ O ₇ Pt
266540	CH ₂ CH ₂ OMe	C ₁₂ H ₂₂ N ₂ O ₆ Pt

SOURCE – SS Pharmaceutical.

REFERENCES

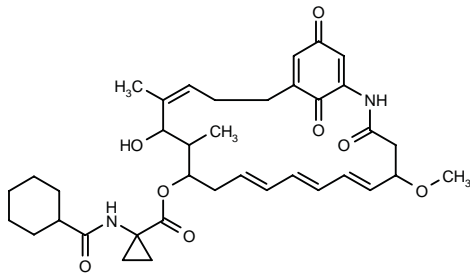
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ANTIBIOTICS AND ALKALOIDS

CYTOTRIENIN IV

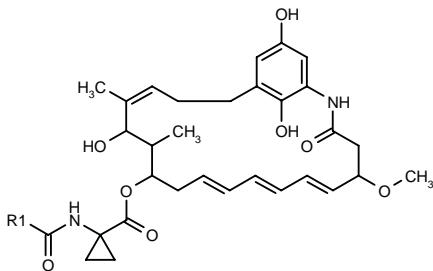
266180

1-(Cyclohexylcarboxamido)cyclopropane-1-carboxylic acid 15-hydroxy-5-methoxy-14,16-dimethyl-3,22,24-trioxo-2-azabicyclo[17.3.1]tetracos-1(23),6(E),8(E),10(E),16,20-hexaen-13-yl ester

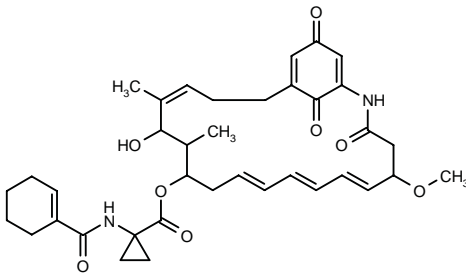


C37 H48 N2 O8; Mol wt: 648.7922

ACTION – Antineoplastic agent isolated from *Streptomyces strain 95-74* (FERM BP-6185) with potent cytotoxicity against human myeloid leukemia K-562 and HL-60 cells (IC₅₀ = 0.001 and 0.001 µg/ml, respectively) and negligible antibacterial activity. Other compounds isolated from the same source are:



Compound	R1	Formula
Cytotrienin I [266998]	1-cyclohexenyl	C ₃₇ H ₄₈ N ₂ O ₈
Cytotrienin II [266999]	cyclohexyl	C ₃₇ H ₅₀ N ₂ O ₈



Cytotrienin III [267000]: C37 H46 N2 O8

SOURCE – Inst. Phys. Chem. Res., Saitama (JP).

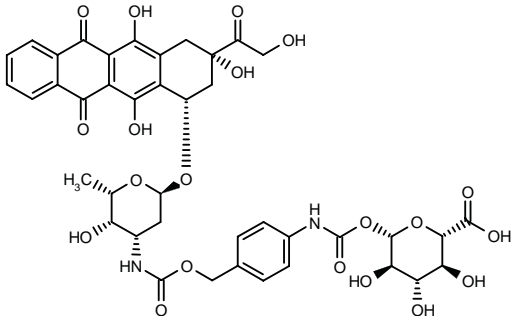
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DOX-GA3

265035

1-O-[N-[4-(4-Demethoxydoxorubicin-N-ylcarbonyl-oxy)methyl]phenyl]carbamoyl]-β-D-glucopyranuronic acid



C41 H42 N2 O20; Mol wt: 882.7768

ACTION – Doxorubicin prodrug that is activated to doxorubicin by β-glucuronidase. Although it was 40-300 times less toxic than doxorubicin *in vitro*, it was superior to the parent drug in inhibiting tumor growth in nude mice bearing human ovarian cancer OVCAR-3 xenografts when given at the maximum tolerated doses (GI = 87% at 2 x 500 mg/kg i.v. on days 0 and 7 vs. 56% at 2 x 8 mg/kg i.v. on days 0 and 7 for doxorubicin). DOX-GA3 was shown to be specifically activated in the tumor, resulting in higher doxorubicin concentrations than following administration of doxorubicin itself, whereas lower levels were detected in plasma, heart and liver. When combined with a conjugate consisting of deglycosylated human β-glucuronidase and the anti-pancarcinoma mono-clonal antibody 323/A3, improved antitumor activity against the ovarian cancer xenografts was obtained compared to both doxorubicin and DOX-GA3, indicating its potential for antibody-directed enzyme prodrug therapy (ADEPT).

SOURCES – Vrije Universiteit, Amsterdam (NL); Univ. Nijmegen (NL).

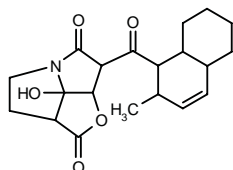
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1. Houba, P.H.J. et al. *Tumor selective activation of a doxorubicin prodrug (DOX-GA3) in human ovarian cancer xenografts*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 194.

UCS-1025A

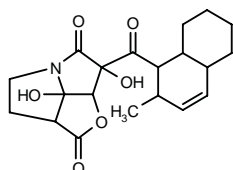
267419

7b-Hydroxy-7-(2-methyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylcarbonyl)perhydrofuro[2,3,4-*gh*]-pyrrolizine-2,6-dione



C₂₀ H₂₅ N O₅; Mol wt: 359.4195

ACTION – Antibacterial and antineoplastic agent produced by *Acremonium* sp. KPC 7629-19 as well as *Humicola* sp. KPC 7781-6. Compound exhibited MIC values of 1.3, 1.3, 1.3 and 5.2 µg/ml, respectively, when tested against *Staphylococcus aureus* ATCC 6538P, *Bacillus subtilis* No. 10707, *Enterococcus hirae* ATCC 10541 and *Proteus vulgaris* ATCC 6897. In addition, it exhibited antiproliferative activity against human mammary carcinoma MCF-7, human cystosarcoma T24, human epidermoid carcinoma A431 and human renal carcinoma ACHN cells (IC₅₀ = 21, 51, 55 and 58 µM, respectively). Another compound isolated from the same source is:



UCS-1025B [267420]: C₂₀ H₂₅ N O₆

SOURCE – Kyowa Hakko.

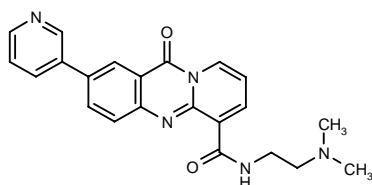
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DNA-INTERCALATING DRUGS

266195

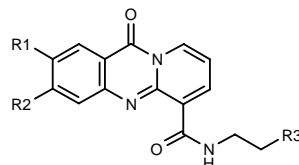
N-[2-(Dimethylamino)ethyl]-11-oxo-2-(3-pyridyl)-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamide



C₂₂ H₂₁ N₅ O₂; Mol wt: 387.4409

ACTION – Antineoplastic agent, an inhibitor of topoisomerase II with *in vitro* cytotoxicity against sensitive and cisplatin-resistant human ovarian carcinoma A2780 and A2780 cells (IC₅₀ = 0.60 and 0.70 µg/ml, respectively). *In vivo* it was effective against murine leukemia P388,

although it was less potent than vincristine (ILS = 37% at 200 mg/kg i.p. vs. 114% for vincristine at 0.8 mg/kg i.p.); when tested in animals bearing murine colon 26 tumors, compound was found to be less potent than doxorubicin (ILS = 64% at 200 mg/kg i.p. vs. 70% for doxorubicin at 4 mg/kg i.p.). Other specifically claimed compounds from this series of pyridoquinazolinone derivatives include the following:



Compound	R1	R2	R3	Formula
267167	4-Pyr	H	N(Me)2	C ₂₂ H ₂₁ N ₅ O ₂
267168	4-Pyr	H	1-pyrrolidinyl	C ₂₄ H ₂₃ N ₅ O ₂
267169	3-quinolinyl	H	N(Me)2	C ₂₆ H ₂₃ N ₅ O ₂
267170	H	3-Pyr	N(Me)2	C ₂₂ H ₂₁ N ₅ O ₂
267171	H	4-Pyr	N(Me)2	C ₂₂ H ₂₁ N ₅ O ₂

SOURCE – American Cyanamid.

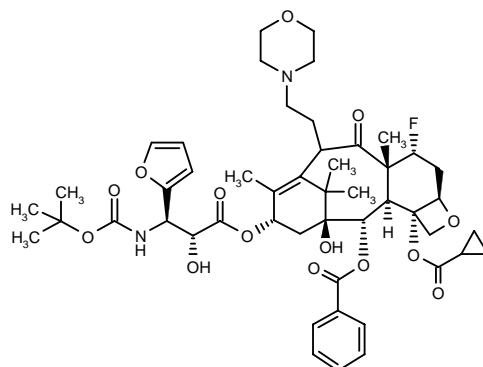
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ANTIMITOTIC DRUGS

265517

[2*aR*]-[2*a*α,4α,4*a*β,6β,9α(2*R*,3*S*),11β,12α,12*a*α,12*b*α]]-12-(Benzoyloxy)-9-[3-(*tert*-butoxycarbonylamino)-3-(2-furyl)-2-hydroxypropionyloxy]-12*b*-(cyclopropylcarbonyloxy)-4-fluoro-11-hydroxy-4*a*,8,13,13-tetramethyl-6-[2-(4-morpholinyl)ethyl]-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-1*H*-7,11-methanocyclodeca-[3,4]benz[1,2-*b*]oxet-5-one



C₄₉ H₆₃ F N₂ O₁₄; Mol wt: 923.0347

ACTION – Antineoplastic agent, a taxane derivative with potent cytotoxicity against murine leukemia P388 and human lung cancer PC-6 and PC-12 cells (GI₅₀ = 0.0159, 0.0925 and 0.0782 ng/ml, respectively).

SOURCE – Daiichi Pharmaceutical.

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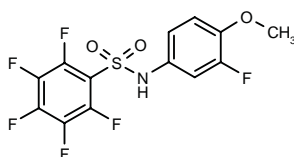
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T-138067

267063

2,3,4,5,6-Pentafluoro-*N*-(3-fluoro-4-methoxyphenyl)-benzenesulfonamide

TI-138067



C13 H7 F6 N O3 S; Mol wt: 371.2563

ACTION – Antineoplastic agent that acts by binding specifically and irreversibly to β -tubulin and disrupting the cell replication process. It is reported to inhibit the growth of human tumor cells in culture including cells expressing the multidrug resistance (MDR) phenotype, and to be effective in delaying tumor growth in SCID mice bearing human tumor xenografts. The compound is currently undergoing phase I clinical trials.

SOURCE – Tularik.

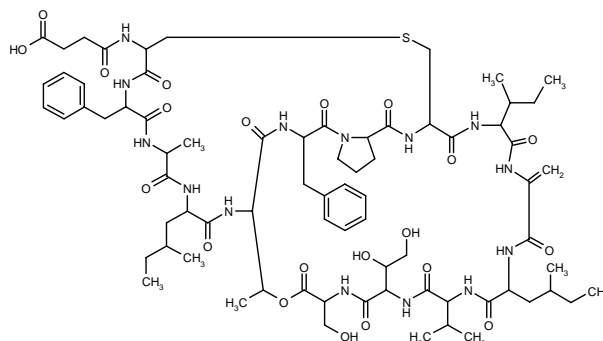
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3. Medina, J.C. et al. *Novel sulfonamides with efficacy against multidrug resistant tumor cells.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 216.
4. *Cancer.* Tularin Web Site 1998, August 27.

VITILEVUAMIDE

264373

30,41-Dibenzyl-27-(3-carboxypropionamido)-8-(1,2-dihydroxyethyl)-5-(hydroxymethyl)-11-isopropyl-2,3,3-dimethyl-14,36-bis(2-methylbutyl)-17-methylene-20-(1-methylpropyl)-3-oxa-35-thia-6,9,12,15,18,21,29,32,35,38,40,43,49-tridecaazatricyclo[21.15.11.0^{43,47}]-nonatetracontane-4,7,10,13,16,19,22,28,31,34,37,39,42,48-tetradecaone



C75 H110 N14 O21 S; Mol wt: 1575.8370

ACTION – Antineoplastic bicyclic peptide isolated from the marine organisms *Didemnum cuculliferum* and *Polysyncraton lithostrotum*, with *in vitro* cytotoxicity against colon cancer HCT116 (IC_{50} = 10 ng/ml), adenocarcinoma A549 (IC_{50} = 0.2 μ g/ml), melanoma SK-MEL-5 (IC_{50} = 0.5 μ g/ml) and kidney cancer A489 cells (IC_{50} = 5 μ g/ml). It was shown to inhibit tubulin polymerization in C6 rat glioma cells at 4 μ g/ml, exhibiting the same effect as colchicine at 25 μ g/ml. *In vivo*, it increased the life span of mice bearing P388 leukemia at 0.03 mg/kg i.p. on days 1, 5 and 9 after tumor implantation (ILS = 70%), while it proved toxic at higher doses (0.06 and 0.13 mg/kg i.p.).

SOURCE – University of Utah Research Foundation, Salt Lake City, UT (US).

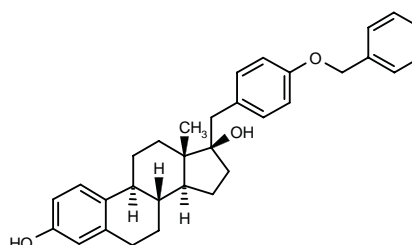
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HORMONAL AGENTS

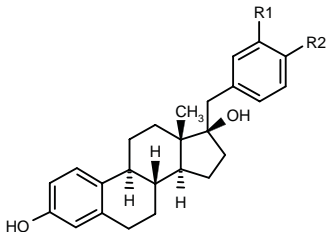
265415¹

17-[4-(Benzyloxy)benzyl]estra-1,3,5(10)-triene-3,17 β -diol



C32 H36 O3; Mol wt: 468.6334

ACTION – Potent inhibitor of estrone sulfotransferase (IC_{50} = 22 nM), being about 300-fold more potent than the substrate estrone sulfate itself, potentially useful in the treatment of estrogen-dependent breast cancer. Other members of this new family of estrone sulfotransferase inhibitors are:



Compound	R1	R2	Formula
265416	Br	H	C ₂₅ H ₂₉ BrO ₂
265417	H	t-Bu	C ₂₉ H ₃₈ O ₂

SOURCE – Laval University, Quebec (CA).

REFERENCES

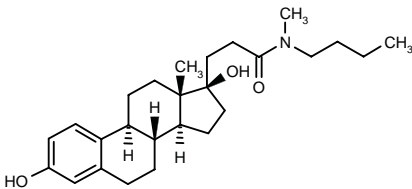
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2. Poirier, D. and Boivin, R.P. A new family of estrone-sulfatase inhibitors. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 278.

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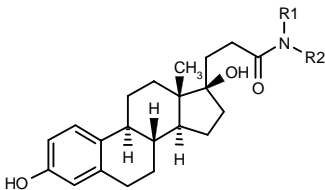
265418

N-Butyl-3-[3,17β-dihydroxyestra-1,3,5(10)-triene-17-yl]-N-methylpropanamide



C₂₆ H₃₉ N O₃; Mol wt: 413.5981

ACTION – The most potent inhibitor of estrone sulfotransferase (IC_{50} = 85 nM) from a series of 17α-alkylamide derivatives of estradiol. It showed a mixed estrogenic/antiestrogenic profile at a concentration of 1 μM, stimulating the proliferation of estrogen receptor-positive (ER+) ZR-75-1 cells and inhibiting the estradiol stimulation of ER+ cells, although it showed no estrogenic activity at 30 nM. A promising candidate for development for the treatment of estrogen-dependent breast cancer, but further optimization may be necessary to minimize residual estrogenic activity. Other related compounds include the following:



Compound	R1	R2	Formula
265419	C ₆ H ₁₃	Me	C ₂₈ H ₄₃ NO ₃
265420	C ₈ H ₁₇	Me	C ₃₀ H ₄₇ NO ₃
265421	C ₈ H ₁₇	C ₈ H ₁₇	C ₃₇ H ₆₁ NO ₃

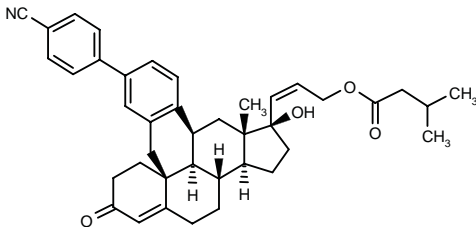
SOURCE – Laval University, Quebec (CA).

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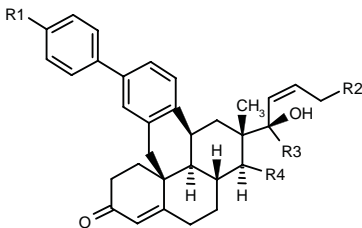
266230

6'-(4-Cyanophenyl)-17β-hydroxy-17α-[3-(3-methylbutyryloxy)-1(Z)-propenyl]-9α,11α-dihydro-4'H-naphtho[3',2',1':10,9,11]estr-4-en-3-one



C₄₀ H₄₅ N O₄; Mol wt: 603.7985

ACTION – Steroid ester progesterone antagonist with significantly improved solubility in comparison with the basic hydroxy compound and enhanced biological activity. It displayed antitumor activity in rats bearing hormone-dependent NMU mammary carcinoma at doses of 0.5 and 5 mg/kg/day p.o. and was also active against tamoxifen-resistant human mammary carcinoma ZR-75 at a dose of 10 mg/kg s.c. Other specifically claimed compounds from this series of steroid esters include the following:



Compound	R1	R2	R3,R4	Formula
267535	CN	i-PrCOOCH ₂	-(CH ₂) ₂ -	C ₄₀ H ₄₅ NO ₄
267536	CN	i-BuCOOCH ₂	-(CH ₂) ₂ -	C ₄₁ H ₄₇ NO ₄
267537	F	i-BuCOOCH ₂	-(CH ₂) ₂ -	C ₄₀ H ₄₇ FO ₄
267538	CN	i-BuCOO	-CH=CH-	C ₄₀ H ₄₃ NO ₄
267539	CN	i-PrCOO	-CH=CH-	C ₃₉ H ₄₁ NO ₄

SOURCE – Schering AG.

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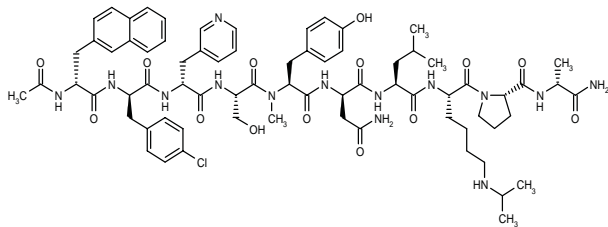
ABARELIX

Prop INN

251979

N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginy-L-leucyl-*N*⁶-isopropyl-L-lysyl-L-prolyl-D-alanylamide

PPI-149
R-3827



C72 H95 Cl N14 O14; Mol wt: 1416.0790

ACTION – Potent luteinizing hormone-releasing hormone (LHRH, GnRH) antagonist with high water solubility and low histamine release-inducing activity. It is currently in late phase II clinical trials for the treatment of prostate cancer. A sustained-release depot formulation has been developed.

SOURCES – Synthélabo; Praecis; Roche.

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12. *Proposed international nonproprietary names (Prop. INN): List 78.* WHO Drug Inf 1997, 11(4): 266.

13. *Roche strengthens oncology portfolio with novel compound for prostate cancer.* F. Hoffmann-La Roche, Ltd. Press Release 1998, June 17.

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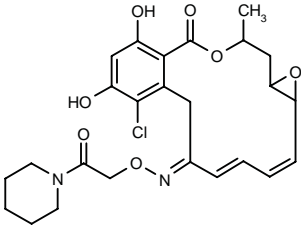
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MONOGRAPH – Graul, A. et al. *Abarelix.* Drugs Fut 1998, 023(10): 1057.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

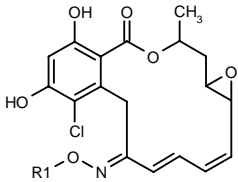
265114

13-Chloro-5,6-epoxy-4,16-dihydroxy-11-[2-oxo-2-(1-piperidinyl)ethoxyimino]-3,4,5,6,11,12-hexahydro-1*H*-2-benzoxacyclotetradecin-1-one



C25 H29 Cl N2 O7; Mol wt: 504.9641

ACTION – Antineoplastic and immunosuppressive agent, an inhibitor of tyrosine kinase activity with antiproliferative activity *in vitro* in rat fibroblast 3Y1-B cells and v-src oncogene-transformed 3Y1-B cells (IC₅₀ = 0.008 and < 0.004 μM, respectively). *In vivo*, compound was shown to reduce tumor growth in mice bearing human breast cancer MX-1 xenografts, giving a T/C x 100of 3% when given at 100 mg/kg/day i.v. x 5 days. Within this series of radicicol derivatives, the following are also included:



Compound	R1	Formula
267434	4-morpholinyl-COCH2	C ₂₄ H ₂₇ ClN ₂ O ₈
267435	2-Pyr-CH2	C ₂₄ H ₂₃ ClN ₂ O ₆
267436	3-Pyr-CH2	C ₂₄ H ₂₃ ClN ₂ O ₆
267437	2-oxo-1-pyrrolidinyl-CH2CH2	C ₂₄ H ₂₇ ClN ₂ O ₇
268758	CO2Et	C ₂₁ H ₂₂ ClNO ₈

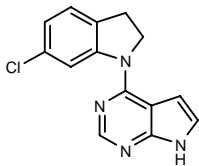
SOURCE – Kyowa Hakko.

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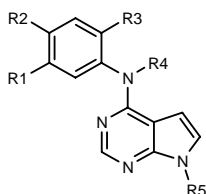
266191

4-(6-Chloro-2,3-dihydro-1*H*-indol-1-yl)-7*H*-pyrrolo[2,3-*d*]-pyrimidine

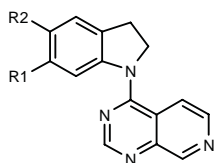


C14 H11 Cl N4; Mol wt: 270.7219

ACTION – Agent for the treatment of cancer and other hyperproliferative disorders such as benign prostatic hyperplasia and psoriasis that acts by inhibiting protein tyrosine kinases of the erbB family such as epidermal growth factor (EGF) receptor, erbB2, HER3 or HER4 tyrosine kinases. Within this series of fused bicyclic pyrimidine derivatives, the following compounds are also specifically claimed:



Compound	R1	R2	R3	R4	R5	Formula
268849	Me	H	-(CH2)2-	H	H	C ₁₅ H ₁₄ N ₄
268850	Cl	F	-(CH2)2-	H	H	C ₁₄ H ₁₀ ClFN ₄
268855	Me	H	H	H	Ac	C ₁₅ H ₁₄ N ₄ O



Compound	R1	R2	Formula
268851	Cl	H	C ₁₅ H ₁₁ ClN ₄
268852	Br	Cl	C ₁₅ H ₁₀ BrClN ₄
268853	F	Cl	C ₁₅ H ₁₀ ClFN ₄
268854	I	H	C ₁₅ H ₁₁ IN ₄

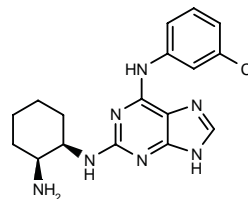
SOURCE – Pfizer.

REFERENCES

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CGP-74514**267064**

cis-*N*²-(2-Aminocyclohexyl)-*N*⁶-(3-chlorophenyl)-9*H*-purine-2,6-diamine



C17 H20 Cl N7; Mol wt: 357.8470

ACTION – Potent and selective inhibitor of the cyclin-dependent kinases CDK1 and CDK2 (IC₅₀ = 0.016 and 0.009 μM, respectively, vs. 6.1 μM for protein kinase C) derived from olomoucine, potentially useful as an antineoplastic agent.

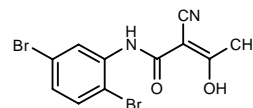
SOURCE – Novartis.

REFERENCES

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LFM-A13**267145**

(*Z*)-2-Cyano-*N*-(2,5-dibromophenyl)-3-hydroxy-2-butenamide



C11 H8 Br2 N2 O2; Mol wt: 360.0042

ACTION – Leflunomide analog with inhibitory activity against Btk tyrosine kinase, proven to induce apoptosis in leukemia cells.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

REFERENCES

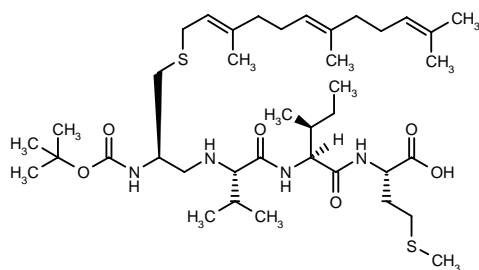
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PS-724***207956**

2(*R*)-(tert-Butoxycarbonylamino)-3-[3,7,11-trimethyl-2(*E*),6(*E*),10(*E*)-dodecatrienylthio]propyl-L-valyl-L-isoleucyl-L-methionine

tert-Butoxycarbonyl—L-(*S*-farnesyl)cysteinyl-ψ(CH₂NH)-L-valyl-L-isoleucyl—L-methionine

P-724



C39 H70 N4 O6 S2; Mol wt: 755.1360

ACTION – Potent and selective inhibitor of Ras endoprotease (IC₅₀ = 10 nM, K_i = 86 nM) with no activity against protein farnesyltransferase.

SOURCES – Harvard College, Cambridge, MA (US); ProScript.

REFERENCES

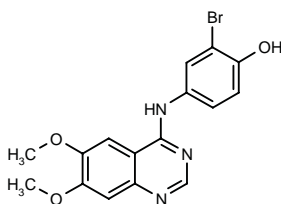
1. Rando, R.R. (Harvard College) *Cpds. for inhibition of proteolysis*. WO 9401126.
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*Identified compound **207956** (see **206291**) Drug Data Report 1994, 016(06): 0589.

WHI-P154²⁻⁵**266241**

4-(3-Bromo-4-hydroxyphenylamino)-6,7-dimethoxyquinazoline

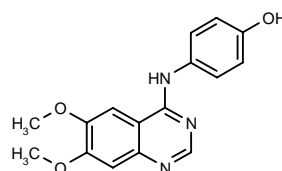
2-Bromo-4-(6,7-dimethoxyquinazolin-4-ylamino)phenol



C16 H14 Br N3 O3; Mol wt: 376.2086

M.p. 233.0-233.5 °C.

ACTION – Antiproliferative agent, an inhibitor of JAK3 and epidermal growth factor (EGF) receptor protein tyrosine kinase, as well as Src tyrosine kinases, with potent cytotoxic activity against human glioblastoma cells. It exhibits significant cytotoxicity against human glioblastoma U373 and U87 cells, inducing apoptosis at micromolar concentrations. Its activity against glioblastoma cells was markedly enhanced and rendered selective by conjugation with EGF, killing the cells at nanomolar concentrations. *In vivo*, EGF-WHI-P154 induced delay in tumor progression and increased tumor-free survival in SCID mice bearing human glioblastoma U373 xenografts at nontoxic doses. Another quinazoline derivative is:



WHI-P131 [267144]¹⁻⁵: C16 H15 N3 O3
DDE-9501

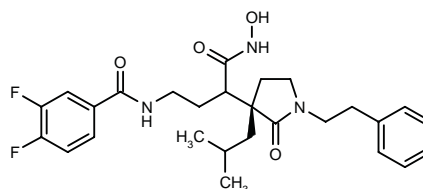
SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

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3. Narla, R.K. et al. *4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline: A novel quinazoline derivative with potent cytotoxic activity against human glioblastoma cells*. Clin Cancer Res 1998, 4(6): 1405.
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ANTIANGIOGENIC AGENTS**PNU-144113****266871**

2-[2-(3,4-Difluorobenzoylamino)ethyl]-*N*-hydroxy-2-[3(*S*)-isobutyl-2-oxo-1-(2-phenylethyl)-3-pyrrolidinyl]acetamide



C27 H33 F2 N3 O4; Mol wt: 501.5707

ACTION – Lactam hydroxamate inhibitor of matrix metalloproteinases (MMPs) with improved stability and increased enzyme-inhibitory activity relative to PNU-142485.

SOURCE – Pharmacia & Upjohn.

REFERENCES

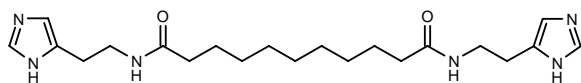
1. Jacobsen, E.J. (Pharmacia AB) *Hydroxamic acid derivs. for use with the treatment of diseases related to connective tissue degradation*. US 5712300, WO 9732846.

2. Hendges, S.K. et al. *Novel lactam hydroxamates as inhibitors of matrix metalloproteinases*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 002.

S-30372

266630

N,N'-Bis[2-(1*H*-imidazol-5-yl)ethyl]undecanediamide



C21 H34 N6 O2; Mol wt: 402.5396

ACTION – Matrix metalloproteinase (gelatinase) inhibitor with zinc-chelating properties shown to have antiinvasive effects in the Matrigel invasion chamber assay in NIH 3T3 fibroblasts, Lewis lung carcinoma, EJ138 bladder carcinoma and HT1080 fibrosarcoma cells.

SOURCE – Servier.

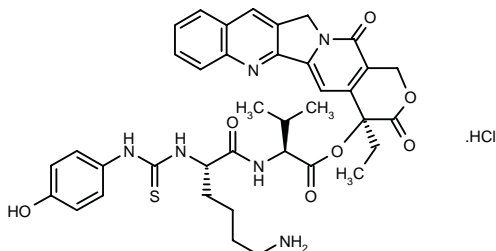
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MISCELLANEOUS ANTINEOPLASTIC AGENTS

264443

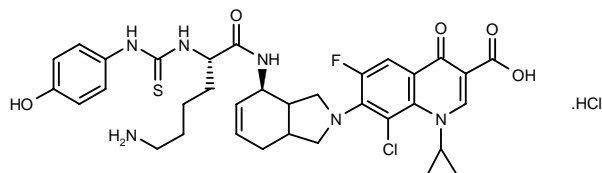
N^α-[*N*-(4-Hydroxyphenyl)thiocarbamoyl]-L-lysyl-L-valine 4(*S*)-ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-4-yl ester hydrochloride



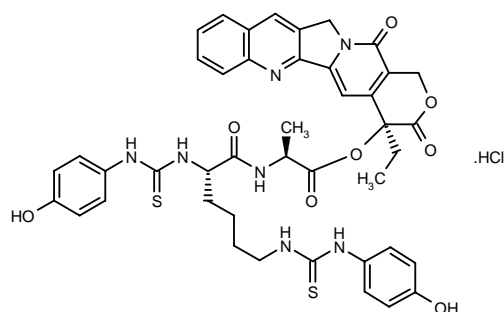
C38 H42 N6 O7 S . HCl; Mol wt: 763.3117

ACTION – Camptothecin conjugate with potent *in vitro* cytotoxicity against human colon tumor SW480 and HT29 cells and murine melanoma B16F10 cells (IC₅₀ = 0.3, 0.2 and 0.6 μM, respectively). *In vitro*, compound was also shown to inhibit the granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced proliferation of bone marrow stem cells with an IC₅₀ value of 10 ng/ml compared to 0.4 ng/ml for camptothecin. When tested *in vivo* in nude mice bearing human lung tumor LXFL 529

xenografts, compound exhibited potent antitumor activity, as shown by a tumor volume on day 21 of 0.2% relative to that of day 0 when given at the maximum tolerated dose of 6.25 mg/kg/day i.p. x 3 days. Within this series of conjugates of known antitumor agents, the following are also included:



267609: C34 H38 Cl F N6 O5 S . HCl



267610: C43 H43 N7 O8 S2 . HCl

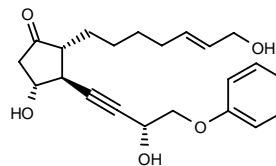
SOURCE – Bayer.

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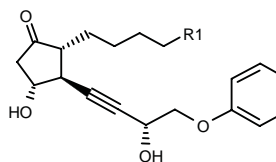
265922

(2*E*)-2-Decarboxy-2-(hydroxymethyl)-16-phenoxy-17,18,19,20-tetranor-2,3,13,14-tetradehydroprostaglandin E₁



C22 H28 O5; Mol wt: 372.4582

ACTION – Antineoplastic agent, a prostaglandin E₁ (PGE₁) analog with selective affinity for prostanoid EP₃ receptors (IC₅₀ = 15.2 nM) relative to EP₁, EP₂ and EP₄ receptor subtypes (IC₅₀ = 719, > 10,000 and > 10,000 nM, respectively). Other compounds from this series of PGE₁ derivatives include the following:



Compound	R1	Formula
266541	(E)-CH=CHCH2OMe	C ₂₃ H ₃₀ O ₅
266542	(CH2)3NO2	C ₂₂ H ₂₉ NO ₆

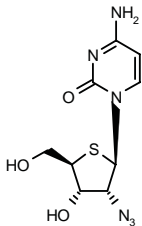
SOURCE – Taisho.

REFERENCES

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265926

2'-Azido-2'-deoxy-4'-thiocytidine



C9 H12 N6 O3 S; Mol wt: 284.2988

ACTION – Antineoplastic and antiviral cytosine derivative.

SOURCE – Yamasa Shoyu.

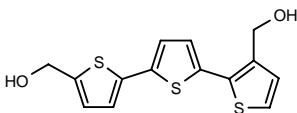
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NSC-658875

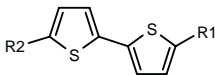
266165

3,5"-Bis(hydroxymethyl)-2,2':5',2"-terthiophene



C14 H12 O2 S3; Mol wt: 308.4448

ACTION – Antineoplastic agent that exhibits selective cytotoxic activity against *ras*-transformed human cells, as shown by GI₅₀ values of 0.002 and 9.7 µg/ml, respectively, against *ras*-transformed and normal human bronchial epithelial cells. A representative compound from a series of polythiophene derivatives, wherein the following are also included:



Compound	R1	R2	Formula
NSC-637393 [266858]	CHO	2-thienyl	C ₁₃ H ₈ OS ₃
NSC-652866 [266859]	CH2NH2	2-thienyl	C ₁₃ H ₁₁ NS ₃
NSC-658879 [266860]	CHO	4-(CH2OH)-2-thienyl	C ₁₄ H ₁₀ O ₂ S ₃
NSC-658878 [266861]	CH2OH	4-(CH2OH)-2-thienyl	C ₁₄ H ₁₂ O ₂ S ₃
NSC-660643 [266862]	CHO	3-thienyl	C ₁₃ H ₈ OS ₃
NSC-660644 [266863]	CH2OH	3-thienyl	C ₁₃ H ₁₀ OS ₃

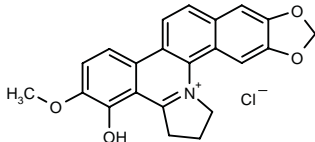
SOURCES – Industrial Technology & Research Institute, Hsinchu (TW); Purdue Research Foundation, West Lafayette, IN (US).

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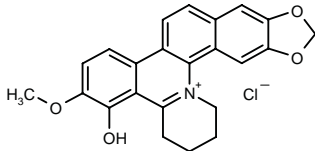
266192

4-Hydroxy-5-methoxy-2,3-dihydro-1*H*-1,3-benzodioxolo-[5,6-*c*]pyrrolo[1,2-*f*]phenanthridinium chloride



C22 H18 Cl N O4; Mol wt: 395.8402

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against human uterine cancer HeLa S3 cells (IC₅₀ = 0.17 µM). Compound also showed antitumor activity *in vivo*, increasing survival of mice bearing P388 leukemia from 8.4 to > 30 days at 75 mg/kg i.v. No deaths occurred following administration of a single dose of 100 mg/kg i.v. to mice. Another compound from this series of phenanthridinium derivatives is:



267070: C23 H20 Cl N O4

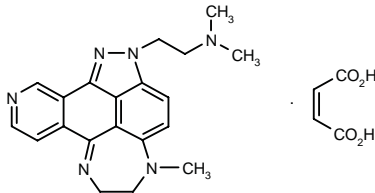
SOURCE – Nippon Kayaku.

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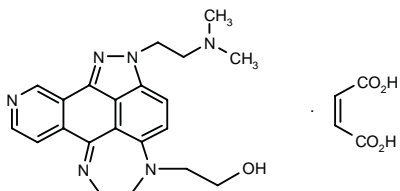
266196

7-[2-(Dimethylamino)ethyl-4-methyl-2,3,4,7-tetrahydropyrazolo[3',4',5':4,5]pyrido[4',3':2,3]naphtho[1,8-*ef*][1,4]-diazepine maleate



C20 H22 N6 . C4 H4 O4; Mol wt: 462.5074

ACTION – Antineoplastic agent with *in vitro* cytotoxicity against human colon adenocarcinoma LoVo cells (IC_{50} = 0.02 μ g/ml). *In vivo*, activity was demonstrated by the ability to prolong the survival time of rats bearing P388 leukemia ($T/C \times 100$ = 162% at 1 mg/kg i.v.), with no toxicity. Another compound from this series of 2,3,4,7-tetrahydropyridoindazole[1,4]benzodiazepine derivatives is:



267080: C21 H24 N6 O . C4 H4 O4

SOURCE – Roche.

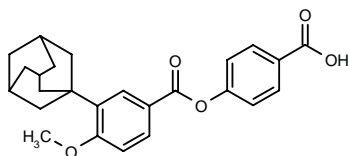
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CD-1599*

152952

4-[3-(1-Adamantyl)-4-methoxybenzoyloxy]benzoic acid



C25 H26 O5; Mol wt: 406.4754

ACTION – Retinoic acid receptor (RAR) agonist with AC_{50} values of 1.3, 8.1 and 6.5 nM for RAR α , RAR β and RAR γ receptors, respectively, in a transactivation assay. Potentially useful for the treatment of acne and promyelocytic leukemia.

SOURCE – Galderma.

REFERENCES

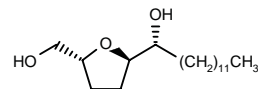
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4. Shroot, B. et al. *Separation of apoptosis-inducing activity from retinoic acid receptor agonist activity by new adamantyl naphtoic acids*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 380.

*Identified compound **152952** Drug Data Report 1989, 011(11): 0947.

DDE-261

267149

(1*R*)-[5(*R*)-(Hydroxymethyl)tetrahydrofuran-2(*R*)-yl]-tridecan-1-ol



C18 H36 O3; Mol wt: 300.4794

ACTION – Antineoplastic agent, an analog of the naturally occurring acetogenin gigantecin with cytotoxicity against a panel of human tumor cell lines such as MDA-MB-231, PC3, SQ20B, U87 and NALM-6 cells (IC_{50} = 49-171 μ M).

SOURCE – Wayne Hughes Institute, Roseville, MN (US).

REFERENCES

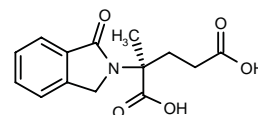
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M-PGA

267065

(-)-(S)-2-Methyl-2-(1-oxo-2,3-dihydro-1*H*-isoindol-2-yl)pentanedioic acid

2-Me-PGA



C14 H15 N O5; Mol wt: 277.2745

ACTION – Antimetastatic agent, a thalidomide analog proven to significantly inhibit (> 90%) pulmonary metastases in a murine B16-BL6 melanoma model after a single oral dose of 0.77 mmol/kg.

SOURCE – EntreMed.

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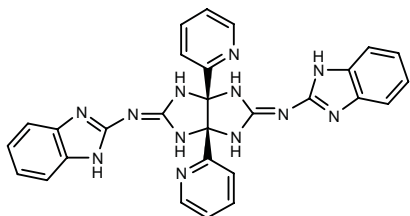
CHEMOPROTECTIVE AGENTS

SB-247464

266243

259023⁺ (as undefined isomer)

cis-2,5-Bis(1*H*-benzimidazol-2-ylimino)-3a,6a-bis(2-pyridyl)perhydroimidazo[4,5-*d*]imidazole



C28 H22 N12; Mol wt: 526.5658

ACTION – Nonpeptide, small-molecule granulocyte colony-stimulating factor (G-CSF) mimic proven to induce tyrosine phosphorylation of the G-CSF receptor, JAK protein tyrosine kinases and STATs (Signal Transducers and Activators of Transcription) in murine myeloid cells, although it was inactive in human myeloid G-CSF-responsive cell lines. It was also found to stimulate the formation of granulocyte colonies in murine bone marrow cells and to increase peripheral blood neutrophil counts in mice, giving a 4-fold increase over baseline at 30 mg/kg b.i.d. s.c., similar to G-CSF at 50 µg/kg b.i.d. s.c. Potentially useful as a lead for the development of orally active cytokine mimics for the treatment of neutropenia associated with cancer chemotherapy.

SOURCE – SmithKline Beecham.

REFERENCES

1. Luengo, J.I. et al. (SmithKline Beecham plc) *Non-peptide G-CSF mimetics*. WO 9744033.
2. Luengo, J.I. et al. *Discovery of a small, non-peptidyl mimic of granulocyte-colony stimulating factor*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst F.2.
3. Tian, S.-S. et al. *A small, nonpeptidyl mimic of granulocyte-colony-stimulating factor*. Science 1998, 257.

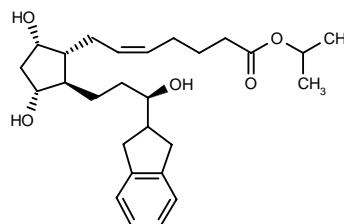
*Drug Data Report 1998, 020(03): 0275.

OCULAR MEDICATIONS

ANTIGLAUCOMA AGENTS

265482

(5*Z*,9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-15-(2-indanyl)-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester



C27 H40 O5; Mol wt: 444.6080

ACTION – Antiglaucoma agent, a conformationally rigid analog of PGF_{2α} shown to exhibit comparable intraocular pressure-lowering activity to PGF_{2α} isopropyl ester and a much lower incidence of ocular side effects.

SOURCE – Alcon.

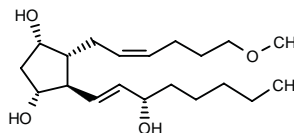
REFERENCES

1. Zinke, P.W. et al. (Alcon Laboratories, Inc.) *Conformationally rigid aryl- or heteroaryl prostaglandins for use in glaucoma therapy*. WO 9821180.

AGN-191129

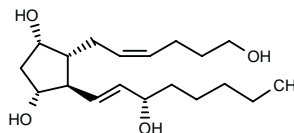
266361

1-Decarboxy-1-methoxyprostaglandin F_{2α}



C20 H36 O4; Mol wt: 340.5004

ACTION – Prostaglandin F_{2α} analog with potent intraocular pressure (IOP)-lowering effects in monkeys with laser-induced ocular hypertension (4.0, 24.6 and 34.9% reduction in IOP at 0.01, 0.1 and 1 mg/ml, respectively) and in ocular normotensive dogs. It induced pupil constriction and hyperemia in dogs, but not in monkeys. The IOP-lowering activity appears to be due to AGN-191129 itself. Another related compound is:



AGN-190910 [266362]: C19 H34 O4

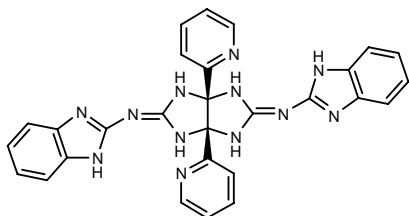
CHEMOPROTECTIVE AGENTS

SB-247464

266243

259023⁺ (as undefined isomer)

cis-2,5-Bis(1*H*-benzimidazol-2-ylimino)-3a,6a-bis(2-pyridyl)perhydroimidazo[4,5-*d*]imidazole



C28 H22 N12; Mol wt: 526.5658

ACTION – Nonpeptide, small-molecule granulocyte colony-stimulating factor (G-CSF) mimic proven to induce tyrosine phosphorylation of the G-CSF receptor, JAK protein tyrosine kinases and STATs (Signal Transducers and Activators of Transcription) in murine myeloid cells, although it was inactive in human myeloid G-CSF-responsive cell lines. It was also found to stimulate the formation of granulocyte colonies in murine bone marrow cells and to increase peripheral blood neutrophil counts in mice, giving a 4-fold increase over baseline at 30 mg/kg b.i.d. s.c., similar to G-CSF at 50 µg/kg b.i.d. s.c. Potentially useful as a lead for the development of orally active cytokine mimics for the treatment of neutropenia associated with cancer chemotherapy.

SOURCE – SmithKline Beecham.

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2. Luengo, J.I. et al. *Discovery of a small, non-peptidyl mimic of granulocyte-colony stimulating factor*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst F.2.
3. Tian, S.-S. et al. *A small, nonpeptidyl mimic of granulocyte-colony-stimulating factor*. Science 1998, 257.

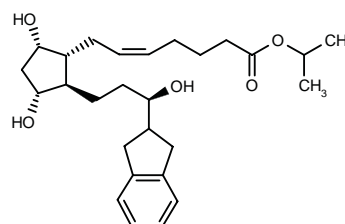
*Drug Data Report 1998, 020(03): 0275.

OCULAR MEDICATIONS

ANTIGLAUCOMA AGENTS

265482

(5*Z*,9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-15-(2-indanyl)-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester



C27 H40 O5; Mol wt: 444.6080

ACTION – Antiglaucoma agent, a conformationally rigid analog of PGF_{2α} shown to exhibit comparable intraocular pressure-lowering activity to PGF_{2α} isopropyl ester and a much lower incidence of ocular side effects.

SOURCE – Alcon.

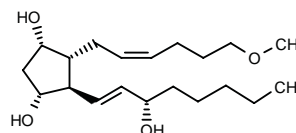
REFERENCES

1. Zinke, P.W. et al. (Alcon Laboratories, Inc.) *Conformationally rigid aryl- or heteroaryl prostaglandins for use in glaucoma therapy*. WO 9821180.

AGN-191129

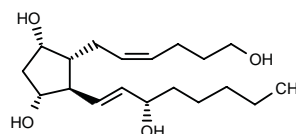
266361

1-Decarboxy-1-methoxyprostaglandin F_{2α}



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ACTION – Prostaglandin F_{2α} analog with potent intraocular pressure (IOP)-lowering effects in monkeys with laser-induced ocular hypertension (4.0, 24.6 and 34.9% reduction in IOP at 0.01, 0.1 and 1 mg/ml, respectively) and in ocular normotensive dogs. It induced pupil constriction and hyperemia in dogs, but not in monkeys. The IOP-lowering activity appears to be due to AGN-191129 itself. Another related compound is:



AGN-190910 [266362]: C19 H34 O4

SOURCE – Allergan.

REFERENCES

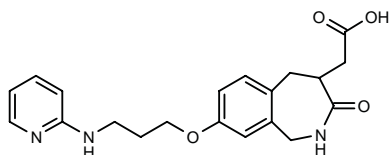
1. Garst, M.E. et al. (Allergan, Inc.) *Cyclopenta(en)ic acid, 2-alkenyl derivs. as therapeutic agents in the treatment of ocular hypertension*. WO 9745405.
2. Chen, J. et al. *Replacement of the carboxylic acid group of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) with neutral substituents provides compounds with unique pharmacology*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 17.33.
3. Woodward, D.F. et al. *Studies on the ocular effects of a pharmacologically novel agent prostaglandin $F_{2\alpha}$ 1-OCH₃ (AGN-191129)*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 17.13.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

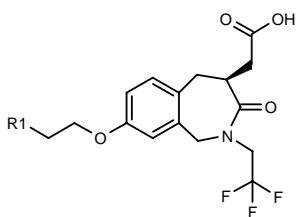
264401

2-[3-Oxo-8-[3-(2-pyridylamino)propoxy]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-4-yl]acetic acid



C₂₀ H₂₃ N₃ O₄; Mol wt: 369.4187

ACTION – Vitronectin ($\alpha_v\beta_3$) receptor antagonist with potential in the treatment of osteoporosis, angiogenesis, tumor growth and metastasis, atherosclerosis, restenosis and inflammation. Other specifically claimed compounds from this series of benzazepine derivatives include the following:



Compound	R1	Formula
266832	2-Pyr-NHCH ₂	C ₂₂ H ₂₄ F ₃ N ₃ O ₄
266833	6-MeNH-2-Pyr	C ₂₂ H ₂₄ F ₃ N ₃ O ₄
266834	4-Me-2-Pyr-NHCH ₂	C ₂₃ H ₂₆ F ₃ N ₃ O ₄

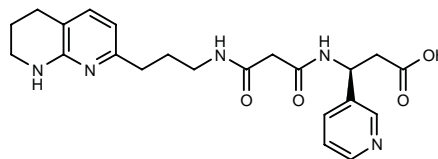
SOURCE – SmithKline Beecham.

REFERENCES

1. Callahan, J.F. et al. (SmithKline Beecham plc) *Vitronectin receptor antagonists*. WO 9814192.

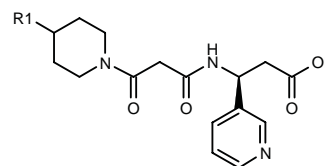
265073

3-(*S*)-(3-Pyridyl)-3-[3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propylamino]malonylamino]propionic acid

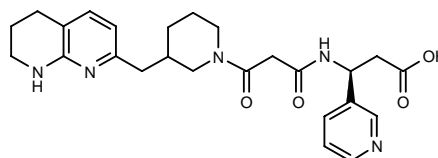


C₂₂ H₂₇ N₅ O₄; Mol wt: 425.4863

ACTION – Nonpeptide integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor), antagonist useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds include the following:



Compound	R2	Formula
267615	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl-CH ₂	C ₂₅ H ₃₁ N ₅ O ₄
267616	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl	C ₂₄ H ₂₉ N ₅ O ₄



267614: C₂₅ H₃₁ N₅ O₄

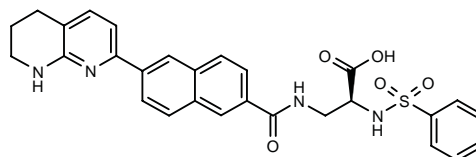
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. and Hartman, G.D. (Merck & Co., Inc.) *Integrin antagonists*. WO 9818460.

265074

2(*S*)-(Phenylsulfonamido)-3-[6-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)naphthalen-2-ylcarboxamido]propionic acid



C₂₈ H₂₆ N₄ O₅ S; Mol wt: 530.6024

ACTION – Nonpeptide integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor), antagonist useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds include the following:

SOURCE – Allergan.

REFERENCES

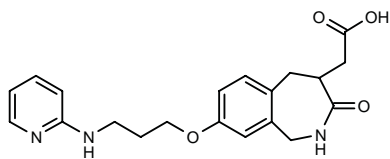
1. Garst, M.E. et al. (Allergan, Inc.) *Cyclopenta(en)ic acid, 2-alkenyl derivs. as therapeutic agents in the treatment of ocular hypertension*. WO 9745405.
2. Chen, J. et al. *Replacement of the carboxylic acid group of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) with neutral substituents provides compounds with unique pharmacology*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 17.33.
3. Woodward, D.F. et al. *Studies on the ocular effects of a pharmacologically novel agent prostaglandin $F_{2\alpha}$ 1-OCH₃ (AGN-191129)*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 17.13.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

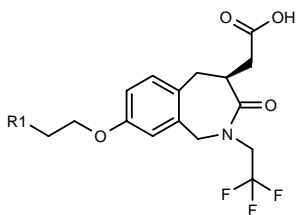
264401

2-[3-Oxo-8-[3-(2-pyridylamino)propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepin-4-yl]acetic acid



C₂₀ H₂₃ N₃ O₄; Mol wt: 369.4187

ACTION – Vitronectin ($\alpha_v\beta_3$) receptor antagonist with potential in the treatment of osteoporosis, angiogenesis, tumor growth and metastasis, atherosclerosis, restenosis and inflammation. Other specifically claimed compounds from this series of benzazepine derivatives include the following:



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266833	6-MeNH-2-Pyr	C ₂₂ H ₂₄ F ₃ N ₃ O ₄
266834	4-Me-2-Pyr-NHCH ₂	C ₂₃ H ₂₆ F ₃ N ₃ O ₄

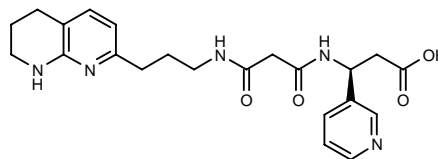
SOURCE – SmithKline Beecham.

REFERENCES

1. Callahan, J.F. et al. (SmithKline Beecham plc) *Vitronectin receptor antagonists*. WO 9814192.

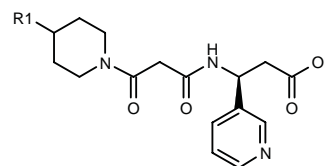
265073

3-(S)-(3-Pyridyl)-3-[3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propylamino]malonylamino]propionic acid

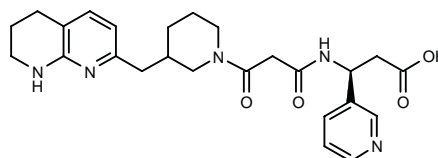


C₂₂ H₂₇ N₅ O₄; Mol wt: 425.4863

ACTION – Nonpeptide integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor), antagonist useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds include the following:



Compound	R2	Formula
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267616	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl	C ₂₄ H ₂₉ N ₅ O ₄



267614: C₂₅ H₃₁ N₅ O₄

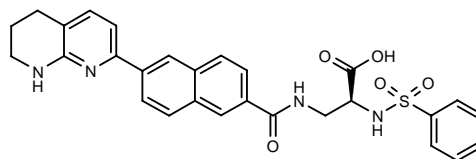
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. and Hartman, G.D. (Merck & Co., Inc.) *Integrin antagonists*. WO 9818460.

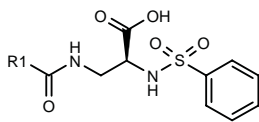
265074

2(S)-(Phenylsulfonamido)-3-[6-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)naphthalen-2-ylcarboxamido]propionic acid



C₂₈ H₂₆ N₄ O₅ S; Mol wt: 530.6024

ACTION – Nonpeptide integrin, particularly $\alpha_v\beta_3$ (vitronectin receptor), antagonist useful for inhibiting bone resorption and in the treatment or prevention of osteoporosis, cancer, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis and inflammation. Other specifically claimed compounds include the following:



Compound	R1	Formula
267617	6-(2-Pyr-NHCH2)-2-Naph	C ₂₆ H ₂₄ N ₄ O ₅ S
267618	4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-Pip	C ₂₃ H ₂₉ N ₅ O ₅ S
267619	6-(2-pyrimidinyl-NHCH2)-2-Naph	C ₂₅ H ₂₃ N ₅ O ₅ S

SOURCE – Merck & Co.

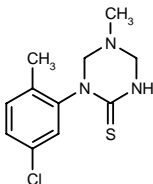
REFERENCES

1. Duggan, M.E. et al. (Merck & Co., Inc.) *Integrin antagonists*. WO 9818461.

TREATMENT OF LIPOPROTEIN DISORDERS

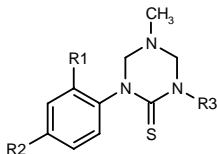
265485

1-(5-Chloro-2-methylphenyl)-5-methylperhydro-1,3,5-triazine-2-thione



C11 H14 Cl N3 S; Mol wt: 255.7716

ACTION – Antiatherosclerotic agent that acts by elevating HDL cholesterol levels, as demonstrated in an *in vivo* assay in cholesterol-fed rats (478% increase in HDL cholesterol levels at 75 mg/kg/day p.o. x 8 days in the diet). A representative compound from a series of substituted tetrahydro-1,3,5-triazin-2-thiones, wherein the following are also included:



Compound	R1	R2	R3	Formula
266773	H	F	H	C ₁₀ H ₁₂ FN ₃ S
266774	H	H	H	C ₁₀ H ₁₃ N ₃ S
266775	H	Cl	H	C ₁₀ H ₁₂ ClN ₃ S
266776	H	NO ₂	H	C ₁₀ H ₁₂ N ₄ O ₂ S
266777	H	CF ₃	H	C ₁₁ H ₁₂ F ₃ N ₃ S
266778	Me	Cl	Me	C ₁₂ H ₁₆ ClN ₃ S

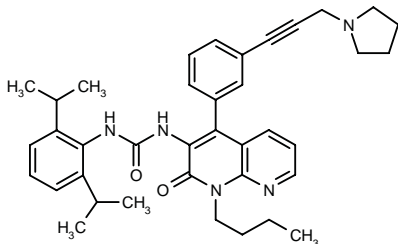
SOURCE – American Home Products.

REFERENCES

1. Memoli, K.A. et al. (American Home Products Corp.) *Substd. tetrahydro-1,3,5-triazin-2[1H]-thiones as anti-atherosclerotic agents*. WO 9821190.

266193

N-[1-Butyl-4-[3-[3-(1-pyrrolidinyl)-1-propynyl]phenyl]-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-*N*'-(2,6-diisopropylphenyl)urea



C38 H45 N5 O2; Mol wt: 603.8065

ACTION – Hypolipidemic and antiatherosclerotic agent, an ACAT inhibitor that exhibits higher potency against enzyme from rat macrophages (96% inhibition at 0.1 μM) than against enzyme from rabbit liver microsomes (39% inhibition at 0.1 μM).

SOURCE – Sumitomo Pharmaceuticals.

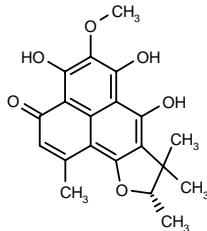
REFERENCES

1. Muraoka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel naphthyridine derivs.* JP 98212288, WO 9823615.

ERABULENOL A

266307

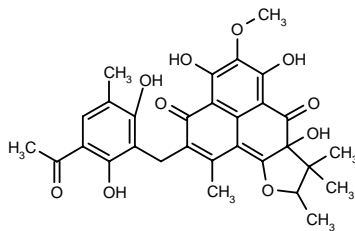
4,6,7-Trihydroxy-5-methoxy-1,8,8,9-(*S*)-tetramethyl-8,9-dihydrophenaleno[1,2-*b*]furan-3-one



C20 H20 O6; Mol wt: 356.3720

Orange powder, [α]_D²³ –220° (c 1.0, MeOH).

ACTION – Inhibitor of cholesteryl ester transfer protein (CETP) produced by *Penicillium* sp. FO-5637, with an IC₅₀ of 47.7 μM against human enzyme and no antimicrobial activity. Another novel compound isolated from the same source is:



Erabulenol B [266308]: C30 H30 O10

SOURCES – Kitasato Institute, Tokyo (JP); Kitasato University, Tokyo (JP).

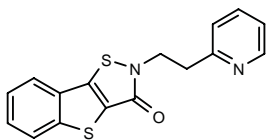
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1. Tabata, N. et al. *Erabulenols, inhibitors of cholesteryl ester transfer protein produced by Penicillium sp. FO-5637. II. Structure elucidation of erabulenols A and B.* J Antibiot 1998, 51(7): 624.
2. Tomoda, H. et al. *Erabulenols, inhibitors of cholesteryl ester transfer protein produced by Penicillium sp. FO-5637. I. Production, isolation and biological properties.* J Antibiot 1998, 51(7): 618.

PD-90524

265034

2-[2-(2-Pyridyl)ethyl][1]benzothieno[2,3-*d*]isothiazol-3(2*H*)-one



C16 H12 N2 O S2; Mol wt: 312.4158

ACTION – An inhibitor of lipoprotein(a) (Lp[a]; IC₅₀ = 1 μM) from a series of isothiazolones that act by inhibiting the coupling of apolipoprotein(a) (apo[a]) to apolipoprotein B-100 (apoB-100) of LDL. Potentially useful for lowering high plasma Lp(a) levels associated with cardiovascular and cerebrovascular disorders.

SOURCE – Warner-Lambert.

REFERENCES

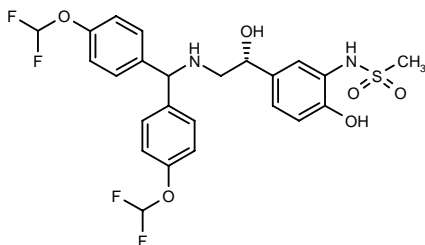
1. Ramharack, R. et al. *Isothiazolones inhibit lipoprotein(a) particle assembly.* 13th Int Symp Drugs Affect Lipid Metab (May 30-June3, Florence) 1998, 95.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

BMS-194449

235524

N-[5-[2-[Bis[4-(difluoromethoxy)phenyl]methylamino]-1(*R*)-hydroxyethyl]-2-hydroxyphenyl]methanesulfonamide



C24 H24 F4 N2 O6 S; Mol wt: 544.5196

ACTION – Selective β₃-adrenoceptor agonist, a clinical candidate for the treatment of obesity and non-insulin-dependent diabetes mellitus (NIDDM).

SOURCE – Bristol-Myers Squibb.

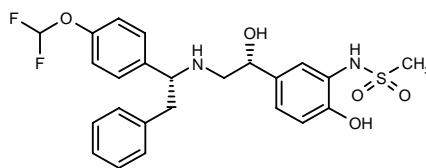
REFERENCES

1. Washburn, W.N. et al. (Bristol-Myers Squibb Co.) *Catecholamine surrogates useful as B3 agonists.* CA 2138675, EP 659737, JP 95206806, US 5776983.
2. Washburn, W.N. et al. *beta 3 Adrenoceptor agonists part I: Program evolution from inception to BMS-194449.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 022.
3. Bristol-Myers Squibb Co. Annual Report 1995.

BMS-196085

235525

N-[5-[2-[1(*R*)-[4-(Difluoromethoxy)phenyl]-2-phenylethylamino]-1(*R*)-hydroxyethyl]-2-hydroxyphenyl]methanesulfonamide



C24 H26 F2 N2 O5 S; Mol wt: 492.5404

ACTION – Potent and selective β₃-adrenoceptor agonist with little or no activity at β₁- or β₂-adrenoceptors, the lead compound in a series of hydroxysulfonanilido-1,2-diarylethylamines selected for further evaluation in clinical trials for potential as an antiobesity and antidiabetic agent.

SOURCE – Bristol-Myers Squibb.

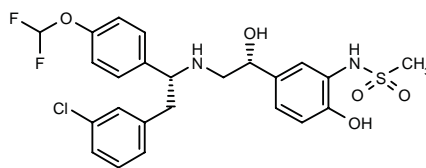
REFERENCES

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2. Gavai, A.V. et al. *β₃ Adrenoceptor agonists part II: Identifications of BMS-196085.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 023.
3. Bristol-Myers Squibb Co. Annual Report 1995.

BMS-210285

266972

N-[5-[2-[2-(3-Chlorophenyl)-1(*R*)-[4-(difluoromethoxy)phenyl]ethylamino]-1(*R*)-hydroxyethyl]-2-hydroxyphenyl]methanesulfonamide



C24 H25 Cl F2 N2 O5 S; Mol wt: 526.9855

ACTION – Potential antiobesity and antidiabetic agent, a preclinical backup compound to BMS-196085 with improved functional selectivity for the β₃-adrenoceptor *in vitro* and *in vivo* in primates.

SOURCE – Bristol-Myers Squibb.

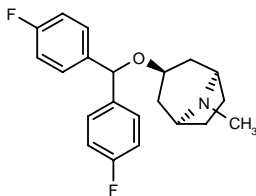
REFERENCES

1. Sher, P.M. et al. β_3 Adrenoceptor agonists part III: Functional selectivity optimization using solid phase parallel array synthesis. From BMS-196085 to BMS-210285. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 024.

TREATMENT OF POISONING AND DRUG DEPENDENCY

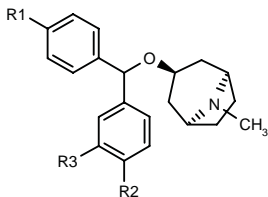
267462

endo-3-[Bis(4-fluorophenyl)methoxy]-8-methyl-8-azabicyclo[3.2.1]octane



C21 H23 F2 N O; Mol wt: 343.4147

ACTION – Agent for the treatment of cocaine addiction, for imaging dopamine transporter/cocaine binding sites and for the diagnosis and monitoring of neurodegenerative disorders, a tropane analog with high affinity for the dopamine transporter and which inhibits dopamine uptake but does not exhibit a cocaine-like behavioral profile. In binding assays, compound exhibited K_i values of 11.8, > 8500, > 2440, 6.1 and 48.8 nM, respectively, for the dopamine, 5-HT and norepinephrine transporters and muscarinic m_1 and m_2 receptors. In addition, it gave an IC_{50} value of 71 nM for inhibition of [3H]-dopamine uptake in rat caudate putamen. In contrast to previous cocaine analogs, compound did not cause discriminative stimulus in rats trained to discriminate cocaine from saline. A representative compound from a series of tropane analogs, wherein the following are also included:



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267465	H	Br	H	C ₂₁ H ₂₄ BrNO
267466	H	F	H	C ₂₁ H ₂₄ FNO
267467	H	Cl	Cl	C ₂₁ H ₂₃ Cl ₂ NO
267468	F	Cl	Cl	C ₂₁ H ₂₂ Cl ₂ FNO

SOURCE – Dept. of Health & Human Services (US).

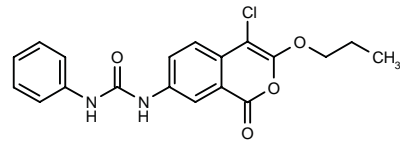
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ICD-1578

266629

N-(4-Chloro-1-oxo-3-propoxy-1 H-2-benzopyran-7-yl)-N'-phenylurea



C19 H17 Cl N2 O4; Mol wt: 372.8063

M.p. 235-6 °C.

ACTION – The most potent antagonist of botulinum toxin B (BoNT/B) light chain (IC_{50} = 27.6 μ M) yet described, a metalloprotease inhibitor previously reported to be highly specific for human leukocyte elastase. It is considered a lead candidate for the development of therapeutic agents for BoNT intoxication.

SOURCES – Dakkro; Georgia Institute of Technology, Atlanta, GA (US); U.S. Army Research Institute of Chemical Defense, MD (US).

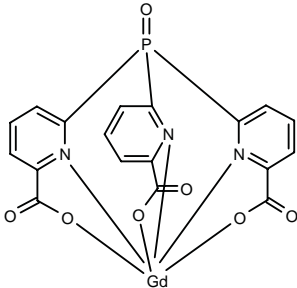
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DIAGNOSTIC AGENTS

265506

[6,6',6''-Phosphoryltris(pyridine- κ N-2-carboxylato- κ O)]-gadolinium(III)



C18 H9 Gd N3 O7 P; Mol wt: 567.5071

ACTION – Contrast agent for use in magnetic resonance imaging (MRI) and X-ray imaging procedures.

SOURCE – Bristol-Myers Squibb.

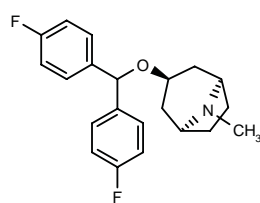
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TREATMENT OF POISONING AND DRUG DEPENDENCY

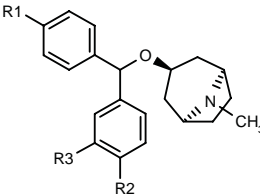
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267468	F	Cl	Cl	C ₂₁ H ₂₂ Cl ₂ FNO

SOURCE – Dept. of Health & Human Services (US).

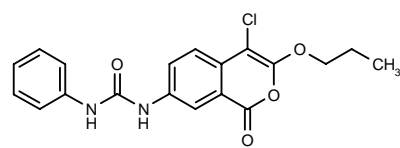
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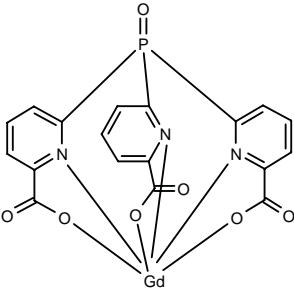
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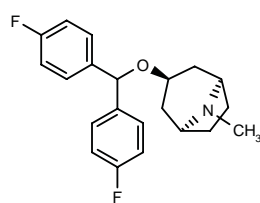
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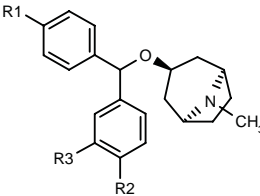
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267468	F	Cl	Cl	C ₂₁ H ₂₂ Cl ₂ FNO

SOURCE – Dept. of Health & Human Services (US).

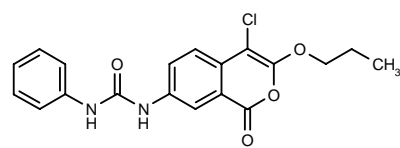
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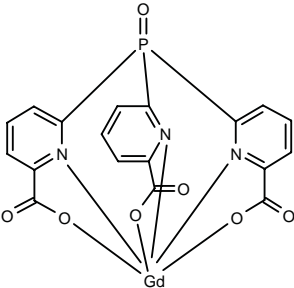
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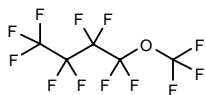
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Peng, W.-J. and Aguilar, D.A. (Hoechst Marion Roussel, Inc.) *MRI contrast agents and ligands*. WO 9822148.

266169

Perfluoro methyl butyl ether



C₅ F₁₂ O; Mol wt: 304.0300

ACTION – Perfluorinated ether-filled vesicle for use as a contrast agent for diagnostic imaging, for example in ultrasound, computed tomography and magnetic resonance imaging.

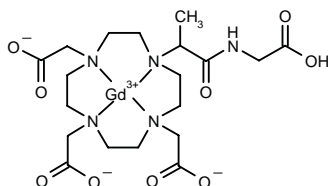
SOURCE – ImaRx.

REFERENCES

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267447

[2,2',2''-[10-[1-[N-(Carboxymethyl)carbamoyl]ethyl]-1,4,7,10-tetraazacyclododecan-1,4,7-triyl]tris(acetato)] gadolinium



C₁₉ H₃₀ Gd N₅ O₉ ; Mol wt: 629.7220

ACTION – Macrocyclic metal complex useful as a contrast agent for NMR or X-ray diagnostic techniques.

SOURCE – Schering AG.

REFERENCES

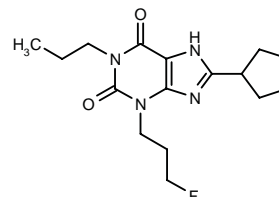
1. Platzek, J. et al. (Schering AG) *Macrocyclic metal complex carboxylic acids, use and method for the production thereof*. WO 9824774.

CPFPX

263714

8-Cyclopentyl-3-(3-fluoropropyl)-1-propyl-3,7-dihydro-1H-purine-2,6-dione

8-Cyclopentyl-3-(2-fluoropropyl)-1-propylxanthine



C₁₆ H₂₃ F N₄ O₂; Mol wt: 322.3817

White crystals, m.p. 190-3 °C.

ACTION – Adenosine A₁ receptor antagonist ($K_i = 0.183$ nM for inhibition of [³H]-CPX binding in bovine brain cortex membranes) that appears to be useful as a radioligand in PET (positron emission tomography) and SPET (single-photon emission tomography) imaging of the receptor when labeled with fluorine-18 ([¹⁸F]).

SOURCES – Forschungszentrum Jülich; Ruprecht-Karls Universität Heidelberg, Heidelberg (DE); University of South Florida, Tampa, FL (US).

REFERENCES

1. Boy, C. et al. *In vivo biodistribution of the new A₁ adenosine receptor (A₁AR) antagonist [18F]8-cyclopentyl-1-propyl-3-(3-fluoro-propyl)xanthine ([18F]CPFPX) in healthy primates*. Drug Dev Res 1998, 43(1): Abstr 261.
2. Holschbach, M. et al. *Synthesis and characterization of radiolabeled xanthines: New antagonists for the A₁ adenosine receptor (A₁AR)*. Drug Dev Res 1998, 43(1): Abstr 268.
3. Holschbach, M. et al. *[18F]8-Cyclopentyl-1-propyl-3-(3-fluoropropyl)-xanthine ([18F]CPFPX), a novel A₁ adenosine receptor (A₁AR) antagonist, images the A₁AR in primate brain*. Drug Dev Res 1998, 43(1): Abstr 267.
4. Holschbach, M.H. et al. *A₁ adenosine receptor antagonists as ligands for positron emission tomography (PET) and single-photon emission tomography (SPET)*. J Med Chem 1998, 41(4): 555.

LARC

264897

Liver and Activation Regulated Chemokine

ACTION – Human chemokine useful in the treatment and diagnosis of diseases related to inflammation and immunological reactions with cellular migration-inhibitory activity, as shown in human monocyte-like THP-1 cells and in isolated human peripheral blood monocytes, lymphocytes and granulocytes.

SOURCE – Shionogi.

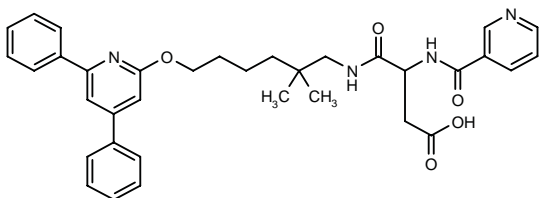
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1. Nimiya, H. et al. (Shionogi & Co. Ltd.) *Novel human CC chemokine LARC*. WO 9817800.

SQ-094

266869

4-[6-(4,6-Diphenyl-2-pyridinyloxy)-2,2-dimethylhexyl-amino]-4-oxo-3-(3-pyridinylcarboxamido)butanoic acid



C35 H38 N4 O5; Mol wt: 594.7082

ACTION – BLT (LTB₄) receptor antagonist (IC₅₀ = 9 nM), potentially useful for detecting sites of inflammation/infection.

SOURCE – DuPont Pharm.

REFERENCES

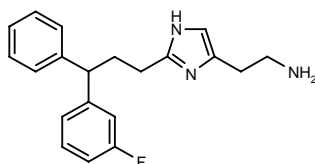
1. Barrett, J.A. et al. (The Du Pont Merck Pharmaceutical Co.) *Radiopharmaceuticals for imaging infection and inflammation*. WO 9815295.

2. Rajopadhye, M. et al. *Leukotriene B4 antagonists with amino acid "east ends" designed for the detection of sites of inflammation/infection*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MED1 005.

PHARMACOLOGICAL TOOLS

266341

2-[2-[3-(3-Fluorophenyl)-3-phenylpropyl]-1H-imidazol-4-yl]-1-ethanamine



C20 H22 F N3; Mol wt: 323.4128

ACTION – Potent partial agonist at histamine H₁ receptors, an analog of histaprodifen with *in vitro* activity comparable to the latter in the guinea pig ileum assay and no effect at other receptors such as histamine H₂ and H₃ and muscarinic M₃ receptors. The compound showed a relative potency compared to histamine (100%) of 154% in the guinea pig aorta assay and of 556% in the rat aorta assay. Potentially useful as a pharmacological tool for the study of histamine H₁ receptor-mediated effects.

SOURCE – Freie Universität Berlin, Berlin (DE).

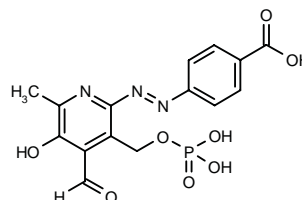
REFERENCES

1. Kramer, K. et al. *Analogues of histaprodifen: Potent partial agonists for histamine H1 receptors*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 9.10.

MRS-2559

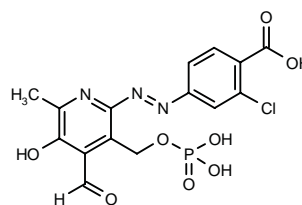
266351

(E)-4-[-2-[4-Formyl-5-hydroxy-6-methyl-3-(phosphonomethyl)-2-pyridyl]diazenyl]benzoic acid



C15 H14 N3 O8 P; Mol wt: 395.2626

ACTION – Selective P2X receptor antagonist, as demonstrated by antagonism of P2X-mediated contractions of guinea pig vas deferens and urinary bladder, with greater effects in vas deferens; it had no effect on P2Y receptor-mediated relaxation of guinea pig taenia coli. Potentially useful as a pharmacological tool for studies on P2 purinoceptors. Another compound from this series of pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid derivatives is:



MRS-2560 [266352]: C15 H13 Cl N3 O8 P

SOURCES – Kazan Medical University, Kazan (RU); National Institutes of Health, Bethesda, MD (US).

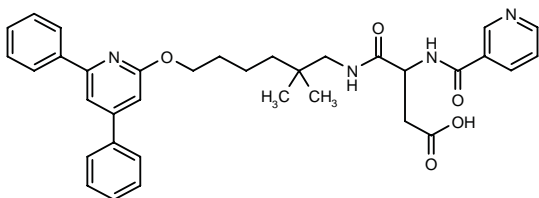
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1. Ziganshin, A.U. et al. *Antagonistic profiles of new derivatives of pyridoxalphosphate-6-azophenyl-2',4'-disulphonic acid*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 10.44.

SQ-094

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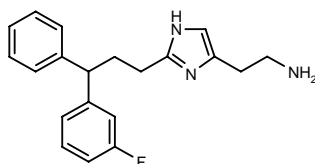
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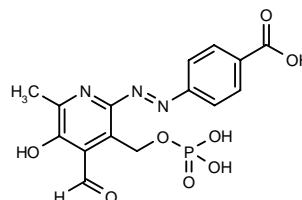
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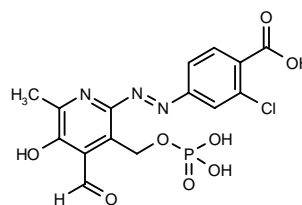
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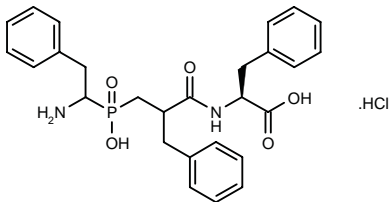
1. Ziganshin, A.U. et al. *Antagonistic profiles of new derivatives of pyridoxal phosphate-6-azophenyl-2',4'-disulphonic acid*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abstr P 10.44.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

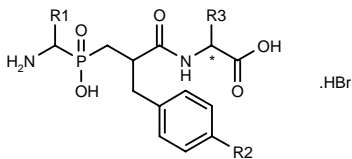
265126^{1,2}

N-[2-[1-Amino-2-phenylethyl(hydroxy)phosphinylmethyl]-3-phenylpropionyl]-L-phenylalanine hydrochloride

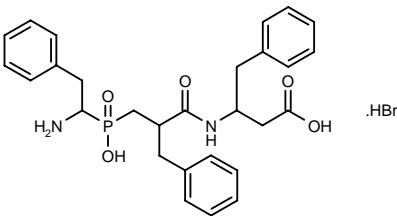


C27 H31 N2 O5 P . HCl; Mol wt: 530.9858

ACTION – Analgesic agent, an orally active dual inhibitor of the enkephalin-degrading enzymes aminopeptidase N and neutral endopeptidase, devoid of the side effects associated with morphine. Also reported to be useful for the treatment of depression, anxiety, sleep disorders, cognitive disorders, hypertension, inflammation and diarrhea. A representative compound from a series of α -aminophosphino peptide derivatives, wherein the following are also included:



Compound	R1	R2	R3	*Isomer	Formula
267717 ¹	CH2Ph	H	i-Bu	S	C ₂₄ H ₃₃ N ₂ O ₅ P.HBr
267718 ¹	CH2Ph	H	4-Ph-PhCH2		C ₃₃ H ₃₅ N ₂ O ₅ P.HBr
267720 ^{1,2}	Me	Ph	Me	S	C ₂₁ H ₂₇ N ₂ O ₅ P.HBr
267721 ¹	i-Bu	H	CH2Ph	S	C ₂₄ H ₃₃ N ₂ O ₅ P.HBr
267722 ¹	Ph	H	Ph		C ₂₅ H ₂₇ N ₂ O ₅ P.HBr
267723 ¹	i-Pr	Ph	Me	S	C ₂₃ H ₃₁ N ₂ O ₅ P.HBr



267719¹: C28 H33 N2 O5 P . HBr

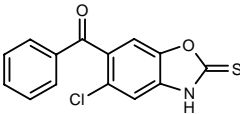
SOURCE – INSERM (FR).

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- Fournie-Zaluski, M.-C. et al. (INSERM [Institut National de la Sante et de la Recherche Medicale]) *Novel (α -aminophosphino) peptide derivs., method for making same and therapeutic applications thereof.* WO 9818803.
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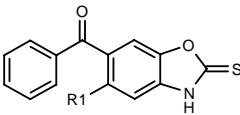
268090

6-Benzoyl-5-chlorobenzoxazole-2(3H)-thione



C14 H8 Cl N O2 S; Mol wt: 289.7412

ACTION – Analgesic agent proven to inhibit phenylbenzoquinone-induced writhing in mice with ED₅₀ values below 30 mg/kg p.o. (ED₅₀ aspirin = 54.5 mg/kg p.o.) and to be at least as active as aspirin against acetic acid-induced writhing. Compound showed antiinflammatory activity in the carrageenan edema model in mice at doses of 25 mg/kg p.o. It is reported to have excellent gastric tolerance. Other specifically claimed substituted 3H-benzoxazole derivatives include the following:



Compound	R1	Formula
268091	H	C ₁₄ H ₉ NO ₂ S
268092	Me	C ₁₅ H ₁₁ NO ₂ S

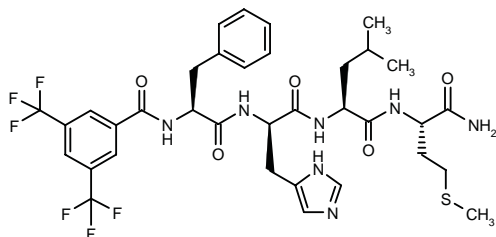
SOURCE – ADIR.

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1. Kalcheva-Batchvarova, V.B. et al. (ADIR et Cie.) *Novel subst. 3H-benzoxazole-2-thiones and 3H-benzothiazole-2-thiones derivs., method for preparing them and pharmaceutical compns. containing them.* WO 9825913.

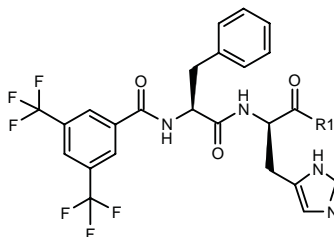
268178

3,5-Bis(trifluoromethyl)benzoyl-L-phenylalanyl-D-histidyl-L-leucyl-L-methioninamide



C35 H41 F6 N7 O5 S; Mol wt: 785.8069

ACTION – Analgesic agent, a substance P (NK₁ receptor) antagonist. Other compounds from this series of 3,5-bis(trifluoromethyl)benzoyl peptides include the following:



Compound	R1	Formula
268179	Leu-NH2	C ₃₀ H ₃₂ F ₆ N ₆ O ₄
268180	NH2	C ₂₄ H ₂₁ F ₆ N ₅ O ₃

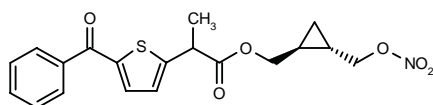
SOURCE – Asahi Glass.

REFERENCES

1. Sakurada, T. et al. (Asahi Glass Co., Ltd.) *NK-1 receptor antagonists.* JP 98182697.

268209

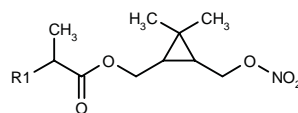
trans-2-(5-Benzoyl-2-thienyl)propionic acid 2-(nitrooxymethyl)cyclopropylmethyl ester



C19 H19 N O6 S; Mol wt: 389.4261

ACTION – Nitrated ester of tiaprofenic acid with comparable analgesic potency but a dissociation between its analgesic and antiinflammatory properties, contrary to parent compound, and which is reported to be devoid of gastrointestinal side effects. Compound exhibited an ED₅₀ value of 0.9 mg/kg p.o. in the acetic acid-induced writhing test in rats and an ED₃₀ value of 10-50 mg/kg p.o. in the carrageenan-induced rat paw edema model, whereas tiaprofenic acid exhibited similar potency in both tests (ED₅₀ = 0.8 mg/kg p.o.; ED₃₀ = 1 mg/kg p.o.). Other

specifically claimed compounds from this series of esters of nitrated cycloaliphatic alcohols include the following:



Compound	R1	Isomer	Formula
268210	5-(PhCO)-2-thienyl	trans	C ₂₁ H ₂₃ NO ₆ S
268211	5-(PhCO)-2-thienyl	cis	C ₂₁ H ₂₃ NO ₆ S
268212	6-MeO-2-Naph	trans	C ₂₁ H ₂₅ NO ₆

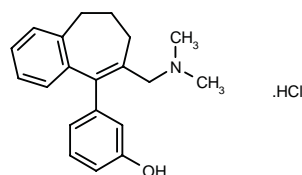
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Droux, S. et al. (Hoechst Marion Roussel, SA) *Analgesic, anti-inflammatory and anti-thrombosis esters of nitrated cycloaliphatic alcohols.* WO 9825918.

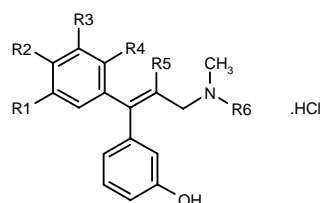
268594

3-[6-(Dimethylaminomethyl)-8,9-dihydro-7H-benzocyclohepten-5-yl]phenol hydrochloride



C20 H23 N O . HCl; Mol wt: 329.8686

ACTION – Analgesic agent with high affinity and selectivity for δ-opioid receptors (K_i = 17.2 ± 4.3 nM). A representative compound from a series of substituted amines, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	Formula
268595	H	H	H	-(CH2)3-		CH2CH2Ph	C ₂₇ H ₂₉ NO.HCl
268596	H	H	H	-(CH2)4-		Me	C ₂₁ H ₂₅ NO.HCl
268597	H	OH	H	-(CH2)2-		Me	C ₁₉ H ₂₁ NO ₂ .HCl
268598	OPh	H	H	-(CH2)2-		Me	C ₂₅ H ₂₅ NO ₂ .HCl
268600	H	H	OMe	-(CH2)2-		Me	C ₂₀ H ₂₃ NO ₂ .HCl
268601	Ph	H	H	-(CH2)2-		Me	C ₂₅ H ₂₅ NO.HCl
268602	Bu	H	H	-(CH2)2-		Me	C ₂₃ H ₂₉ NO.HCl
268603	OH	H	H	H	Me	Me	C ₁₈ H ₂₁ NO ₂ .HCl
268604	H	Ph	H	H	Me	Me	C ₂₄ H ₂₅ NO.HCl

SOURCE – Grünenthal.

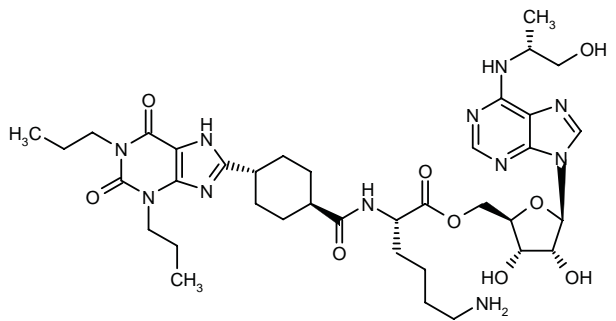
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GP-04012

267566

N-[*trans*-4-(1,3-Dipropylxanthin-8-yl)cyclohexylcarbonyl]-L-lysine *N*⁶-[2-hydroxy-1(*R*)-methylethyl]adenosin-5'-*O*-yl ester



C37 H55 N11 O9; Mol wt: 797.9095

ACTION – Potent adenosine A₁ receptor antagonist from a series of binary compounds, reported to exert analgesic activity at doses not associated with hemodynamic effects.

SOURCE – Metabasis.

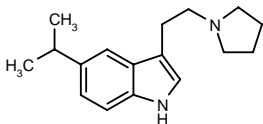
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1. Reddy, K.R. et al. *Adenosine A1 receptor agonist-antagonist binary compounds. III. Therapeutic potential.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 091.

ANTIMIGRAINE DRUGS

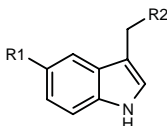
268634

5-Isopropyl-3-[2-(1-pyrrolidinyl)ethyl]-1*H*-indole



C17 H24 N2; Mol wt: 256.3906

ACTION – Antimigraine agent, a 5-HT_{1D}-like receptor agonist with comparable potency to sumatriptan in the rabbit saphenous vein assay (EC₅₀ = 0.25 μM vs. 0.22 μM for sumatriptan). When tested in guinea pigs, it was found to be more potent than sumatriptan in inhibiting neuronal protein extravasation due to stimulation of the trigeminal ganglia. Other compounds from this series of 5-alkyl indoles include the following:



Compound	R1	R2	Formula
268635	t-Bu	1-pyrrolidinyl-CH2	C ₁₈ H ₂₆ N ₂
268636	Me	1-pyrrolidinyl-CH2	C ₁₆ H ₂₀ N ₂
268637	Et	1-Me-2(R)-pyrrolidinyl	C ₁₆ H ₂₂ N ₂

SOURCE – Allelix Biopharmaceuticals.

REFERENCES

1. Slassi, A. et al. (Allelix Biopharmaceuticals Inc.) *5-Alkyl indole cpds. as 5-HT_{1D}-like ligands.* WO 9827089.

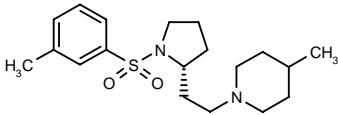
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

SB-258741

267695

4-Methyl-1-[2-[1-(3-methylphenylsulfonyl)pyrrolidin-2(*R*)-yl]ethyl]piperidine



C19 H30 N2 O2 S; Mol wt: 350.5240

ACTION – Potent and selective 5-HT₇ receptor antagonist (pK_i = 8.5) with 300-fold selectivity over a range of other receptors.

This receptor has been implicated in sleep disorders, depression and schizophrenia.

SOURCE – SmithKline Beecham.

REFERENCES

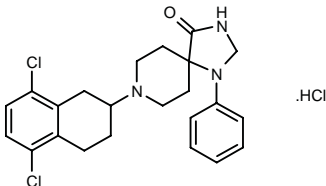
1. Forbes, I.T. et al. (SmithKline Beecham plc) *Sulphonamide derivs. and their use in the treatment of CNS disorders.* WO 9748681.

2. Lovell, P.J. *SB-258741: A novel, potent and selective 5-HT₇ antagonist.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.339.

ANXIOLYTICS

268669

(-)-8-(5,8-Dichloro-1,2,3,4-tetrahydronaphthalen-2-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one hydrochloride

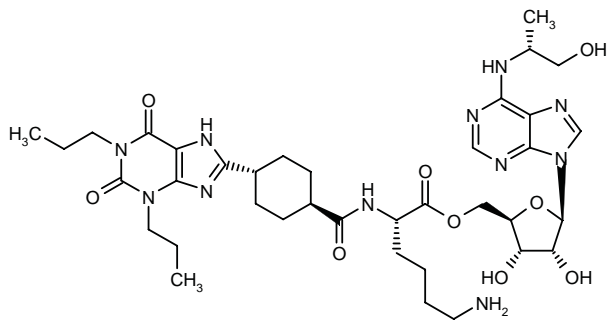


C23 H25 Cl2 N3 O . HCl; Mol wt: 466.8374

GP-04012

267566

N-[*trans*-4-(1,3-Dipropylxanthin-8-yl)cyclohexylcarbonyl]-L-lysine *N*⁶-[2-hydroxy-1(*R*)-methylethyl]adenosin-5'-*O*-yl ester



C37 H55 N11 O9; Mol wt: 797.9095

ACTION – Potent adenosine A₁ receptor antagonist from a series of binary compounds, reported to exert analgesic activity at doses not associated with hemodynamic effects.

SOURCE – Metabasis.

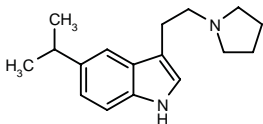
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1. Reddy, K.R. et al. *Adenosine A1 receptor agonist-antagonist binary compounds. III. Therapeutic potential.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 091.

ANTIMIGRAINE DRUGS

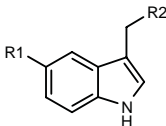
268634

5-Isopropyl-3-[2-(1-pyrrolidinyl)ethyl]-1*H*-indole



C17 H24 N2; Mol wt: 256.3906

ACTION – Antimigraine agent, a 5-HT_{1D}-like receptor agonist with comparable potency to sumatriptan in the rabbit saphenous vein assay (EC₅₀ = 0.25 μM vs. 0.22 μM for sumatriptan). When tested in guinea pigs, it was found to be more potent than sumatriptan in inhibiting neuronal protein extravasation due to stimulation of the trigeminal ganglia. Other compounds from this series of 5-alkyl indoles include the following:



Compound	R1	R2	Formula
268635	t-Bu	1-pyrrolidinyl-CH2	C ₁₈ H ₂₆ N ₂
268636	Me	1-pyrrolidinyl-CH2	C ₁₆ H ₂₀ N ₂
268637	Et	1-Me-2(R)-pyrrolidinyl	C ₁₆ H ₂₂ N ₂

SOURCE – Allelix Biopharmaceuticals.

REFERENCES

1. Slassi, A. et al. (Allelix Biopharmaceuticals Inc.) *5-Alkyl indole cpds. as 5-HT_{1D}-like ligands.* WO 9827089.

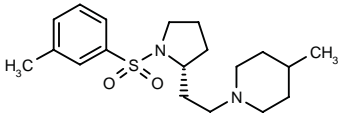
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

SB-258741

267695

4-Methyl-1-[2-[1-(3-methylphenylsulfonyl)pyrrolidin-2(*R*)-yl]ethyl]piperidine



C19 H30 N2 O2 S; Mol wt: 350.5240

ACTION – Potent and selective 5-HT₇ receptor antagonist (pK_i = 8.5) with 300-fold selectivity over a range of other receptors.

This receptor has been implicated in sleep disorders, depression and schizophrenia.

SOURCE – SmithKline Beecham.

REFERENCES

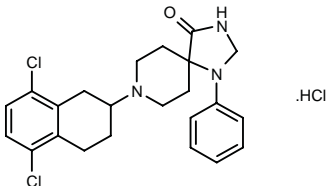
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2. Lovell, P.J. *SB-258741: A novel, potent and selective 5-HT₇ antagonist.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.339.

ANXIOLYTICS

268669

(-)-8-(5,8-Dichloro-1,2,3,4-tetrahydronaphthalen-2-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one hydrochloride



C23 H25 Cl2 N3 O . HCl; Mol wt: 466.8374

ACTION – ORL1 (orphanin FQ, OFQ) receptor ligand potentially useful for the treatment of CNS and other disorders such as anxiety, stress, depression, trauma, memory impairment, epilepsy, acute and/or chronic pain, drug withdrawal symptoms, blood pressure disorders and eating disorders such as obesity. A representative compound from a series of 8-substituted 1,3,8-triazaspiro[4.5]decan-4-one derivatives.

Orphanin FQ, or nociceptin, is a 17-amino-acid peptide that is a natural ligand for a G-protein-coupled receptor found at high levels in brain tissue and that appears to act as a brain neurotransmitter to modulate nociceptive and locomotor behavior.

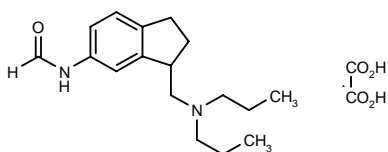
SOURCE – Roche.

REFERENCES

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268680

N-[1-(Dipropylaminomethyl)indan-6-yl]formamide oxalate



C17 H26 N2 O . C2 H2 O4; Mol wt: 364.4392

ACTION – 5-HT_{1A} receptor agonist, as demonstrated *in vitro* in a binding assay (IC₅₀ = 4.1 nM against [³H]-OH-DPAT binding in rat brain membranes; IC₅₀ = 3.5 and 41 nM, respectively, for 8-OH-DPAT and buspirone) and *in vivo* in the 8-OH-DPAT cue model in rats (ED₅₀ = 0.0052 μmol/kg s.c.; ED₅₀ = 0.10 and 0.62 μmol/kg s.c., respectively, for 8-OH-DPAT and buspirone). Compound exhibited no affinity for dopamine D₂ receptors and was shown to be devoid of cataleptogenic effects. It is also reported to exert potent anxiolytic effects in a rat model. Claimed for the treatment of psychosis, anxiety, depression, impulse control disorders, alcohol abuse, aggression, ischemic disorders, side effects induced by conventional antipsychotic agents, as well as cardiovascular disorders.

SOURCE – Lundbeck.

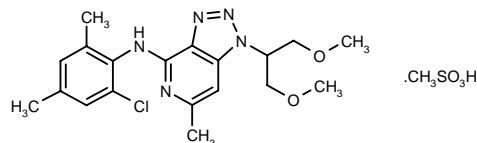
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DMP-695

267442

N-(2-Chloro-4,6-dimethylphenyl)-1-[2-methoxy-1-(methoxymethyl)ethyl]-6-methyl-1*H*-[1,2,3]triazolo[4,5-*c*]pyridin-4-amine methanesulfonate



C19 H24 Cl N5 O2 . C H4 O3 S; Mol wt: 485.9902

ACTION – Orally active corticotropin-releasing factor (CRF) CRF₁ receptor antagonist with potential in the treatment of anxiety and depression.

SOURCE – DuPont Pharmaceuticals.

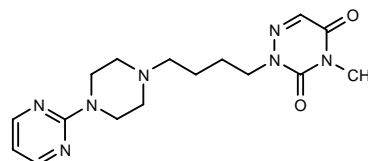
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2. Bakthavatchalam, R. et al. *The discovery of DMP 695: An orally active corticotropin-releasing hormone (CRH1) receptor antagonist.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abstr MEDI 134.

F-11440

267699

4-Methyl-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione



C16 H23 N7 O2; Mol wt: 345.4047

ACTION – Potent, selective and high-efficacy 5-HT_{1A} receptor agonist with anxiolytic and antidepressant activity, currently undergoing clinical development. In binding assays, it gave a pK_i value of 8.33 for 5-HT_{1A} receptors (pK_i buspirone = 7.65; pK_i flesinoxan = 8.91) compared to respective values of 6.16 and 5.75 for α₁-adrenoceptors (pK_i buspirone = 6.19; pK_i flesinoxan = 6.50) and dopamine D₂ receptors (pK_i buspirone = 7.49; pK_i flesinoxan = 7.05); in a functional assay, it decreased the forskolin-induced increase in cAMP in HA7 cells with intrinsic activity equal to that of 5-HT (100% maximum inhibition; buspirone: 49%; flesinoxan: 93%). The compound was highly active in the punished responding test for anxiolytic potential in pigeons (minimum significant dose [MSD] = 0.01 mg/kg p.o.) and in the forced swimming test for antidepressant potential in rats (MSD = 0.16 mg/kg p.o.).

SOURCE – Pierre Fabre.

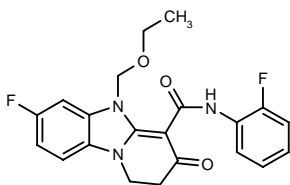
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2. Dupont-Passelaigue, E. et al. *S.A.R. of a novel series of high efficacy 5HT_{1A} agonists with antidepressant and anxiolytic potential*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P. 296.
3. Koek, W. et al. *F 11440, a potent, selective, high efficacy 5-HT_{1A} receptor agonist with marked anxiolytic and antidepressant potential*. J Pharmacol Exp Ther 1998, 287(1): 266.

RWJ-51204

267584

5-(Ethoxymethyl)-7-fluoro-*N*-(2-fluorophenyl)-3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazole-4-carboxamide



C21 H19 F2 N3 O3; Mol wt: 399.3951

ACTION – Anxiolytic agent and anticonvulsant, the lead compound in a series of pyrido[1,2-*a*]benzimidazoles (PBIs) that bind to the benzodiazepine site on the GABA_A receptor (IC₅₀ = 0.14 nM). It was active in a conflict test in rats, with minimum effective doses (MED) of 10 mg/kg i.p. or less and 0.3 mg/kg p.o., and it was also effective in a conflict test in squirrel monkeys at 1 mg/kg p.o. Anticonvulsant activity was demonstrated against pentylenetetrazol-induced convulsions in mice (ED₅₀ = 0.01 mg/kg i.p. and 0.1 mg/kg p.o.).

SOURCE – R.W. Johnson.

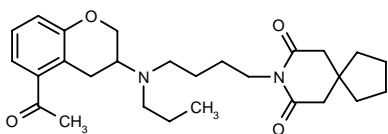
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2. Cesco-Cancian, S. et al. *Process research for the synthesis of RWJ-51204, a novel anxiolytic agent*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 482.

S-23751

267679

8-[4-[*N*-(5-Acetyl-3,4-dihydro-2*H*-1-benzopyran-3-yl)-*N*-propylamino]butyl]-8-azaspiro[4.5]decane-7,9-dione



C27 H38 N2 O4; Mol wt: 454.6072

ACTION – Potent 5-HT_{1A} (K_i = 0.3 ± 0.03 nM for inhibition of [³H]-OH-DPAT binding) and 5-HT₇ (K_i = 3.1 ± 0.7 nM for inhibition of [³H]-lysergic acid diethylamide binding) receptor ligand with anxiolytic activity in the light/dark assay at very low doses.

SOURCE – Servier.

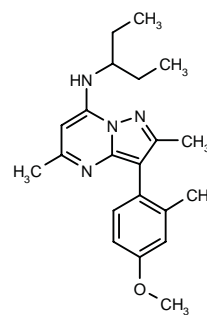
REFERENCES

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SP-904*

261547

7-(1-Ethylpropylamino)-3-(4-methoxy-2-methylphenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine



C21 H28 N4 O; Mol wt: 352.4792

ACTION – High-affinity and selective human corticotropin-releasing factor (CRF) CRF₁ receptor ligand from a series of pyrazolo[1,5-*a*]pyrimidines with potent antagonist activity *in vitro* and high oral bioavailability.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

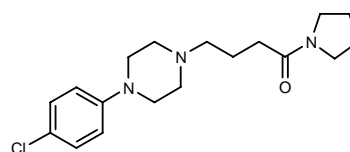
1. Arvanitis, A.G. and Chorvat, R.J. (The Du Pont Merck Pharmaceutical Co.) *Azolo triazines and pyrimidines*. WO 9803510.
2. Gilligan, P.J. et al. *Pyrazolo-[1,5-*a*]pyrimidine CRF antagonists: Synthesis and structure activity relationships*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 135.

*Identified compound **261547** Drug Data Report 1998, 020(05): 0386.

ANTIPSYCHOTIC DRUGS

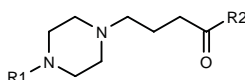
265907

1-(4-Chlorophenyl)-4-[4-oxo-4-(1-pyrrolidinyl)butyl]-piperazine



C18 H26 Cl N3 O; Mol wt: 335.8764

ACTION – Antipsychotic agent expected to be associated with minimal extrapyramidal side effects, a dopamine D₄ receptor antagonist with additional affinity for 5-HT₂ and muscarinic M₁ receptors, and α₁- and α₂-adrenoceptors. A compound within a series of piperazine derivatives wherein the following are also included:



Compound	R1	R2	Formula
266676	4-Cl-Ph	1-azetidiny	C ₁₇ H ₂₄ ClN ₃ O
266677	4-Cl-Ph	3-oxo-8-aza-bicyclo[3.2.1]oct-8-yl	C ₂₁ H ₂₆ ClN ₃ O ₂
266678	4-Cl-Ph	1-aziridiny	C ₁₆ H ₂₂ ClN ₃ O
266679	1-Naph	1-pyrrolidiny	C ₂₂ H ₂₉ N ₃ O
266680	2-Naph	1-Pip	C ₂₃ H ₃₁ N ₃ O
266681	5,6,7,8-tetrahydro-1-Naph	1-azetidiny	C ₂₁ H ₃₁ N ₃ O
266682	2-Pyr	3,3,5-(Me)3-perhydro-1-azepiny	C ₂₂ H ₃₆ N ₄ O

SOURCE – Yoshitomi.

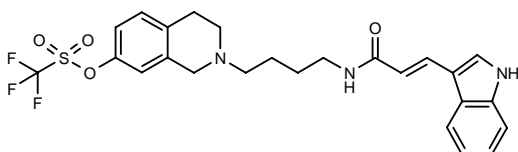
REFERENCES

1. Naka, Y. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Piperazine cpds.* JP 98152470.

267573

Trifluoromethanesulfonic acid 2-[4-[3-(1*H*-indol-3-yl)-2(*E*)-propenoylamino]butyl]-1,2,3,4-tetrahydro-7-isoquinolinyl ester

3-(1*H*-Indol-3-yl)-*N*-[4-[7-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]butyl]-2(*E*)-propenamide



C₂₅ H₂₆ F₃ N₃ O₄ S; Mol wt: 521.5574

ACTION – Potential antipsychotic agent with high affinity and selectivity for the dopamine D₃ receptor (pK_i = 8.4 vs. 6.2 for D₂ receptors). The compound penetrates the brain and shows low blood clearance and a half-life of 2.5 h in rats.

SOURCE – SmithKline Beecham.

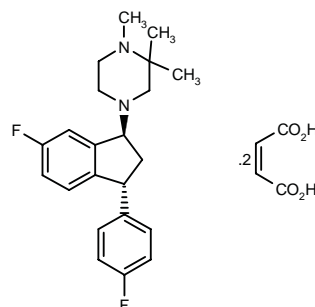
REFERENCES

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2. Stemp, G. et al. *Novel 1,2,3,4-tetrahydroisoquinolines with high affinity and selectivity for the dopamine D₃ receptor.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P. 251.

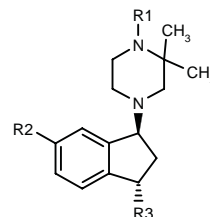
268675

(±)-*trans*-4-[6-Fluoro-3-(4-fluorophenyl)indan-1-yl]-1,2,2-trimethylpiperazine dimaleate



C₂₂ H₂₆ F₂ N₂ . 2 C₄ H₄ O₄; Mol wt: 588.6006

ACTION – Agent for the treatment of CNS disorders such as schizophrenia, anxiety, depression, sleep disturbances, migraine, Parkinson's disease and cocaine abuse with high affinity for dopamine D₁ receptors (IC₅₀ = 0.88 nM) and some degree of selectivity relative to D₂ receptors (IC₅₀ = 11 nM). Additionally, compound exhibited high affinity for 5-HT₂ receptors (IC₅₀ = 3.6 nM) and was found to potently inhibit dopamine uptake (IC₅₀ = 9 nM). *In vivo*, it exhibited potent D₁-antagonist properties, as demonstrated by an ED₅₀ value of 0.50 μmol/kg i.v. against SK&F-38393-induced circling behavior in rats with 6-OHDA lesions, while showing no cataleptogenic potential in rats (ED₅₀ > 68 μmol/kg). Other compounds from this series of 1-piperazino-1,2-dihydroindene derivatives include the following:



Compound	R1	R2	R3	Formula
268676	H	Cl	4-F-Ph	C ₂₁ H ₂₄ ClFN ₂
268677	Me	Cl	Ph	C ₂₂ H ₂₇ ClN ₂
268678	H	Cl	3-thienyl	C ₁₉ H ₂₃ ClN ₂ S
268679	Me	H	4-F-Ph	C ₂₂ H ₂₇ FN ₂

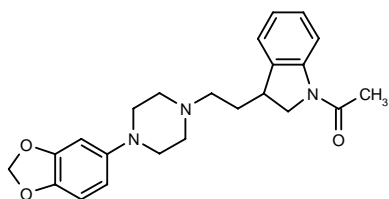
SOURCE – Lundbeck.

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1. Bogeso, K. and Bregnedal, P. (Lundbeck A/S) *1-Piperazino-1,2-dihydroindene derivs.* US 5807855.

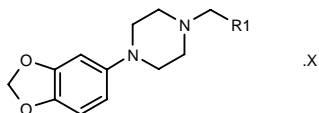
268930

1-[2-(1-Acetylidolin-3-yl)ethyl]-4-(1,3-benzodioxol-5-yl)piperazine



C23 H27 N3 O3; Mol wt: 393.4843

ACTION – Agent with potent and selective affinity for dopamine D₄ receptors (IC₅₀ = 3.7 nM) and weak or no affinity for dopamine D₂ receptors, reported to possess additional affinity for central serotonergic receptors such as 5-HT_{1A} and/or 5-HT_{2A} receptors. Claimed for the treatment of the positive and negative symptoms of schizophrenia and other psychoses, anxiety, panic, obsessive-compulsive disorders, depression, alcohol abuse, aggression, side effects induced by conventional antipsychotic agents, ischemic disorders, migraine, senile dementia, cardiovascular disorders and sleep disorders. Other specifically claimed compounds from this series of indane and dihydroindole derivatives include the following:



Compound	R1	X	Formula
268931	1-indanyl	fumarate	C ₂₁ H ₂₄ N ₂ O ₂ ·C ₄ H ₄ O ₄
268932	6-Br-1-indanyl	fumarate	C ₂₁ H ₂₃ BrN ₂ O ₂ ·C ₄ H ₄ O ₄
268933	1-indanyl-CH ₂	fumarate	C ₂₂ H ₂₆ N ₂ O ₂ ·C ₄ H ₄ O ₄
268934	2,3-dihydro-3-indolyl-COCH ₂ CH ₂	oxalate	C ₂₃ H ₂₇ N ₃ O ₃ ·C ₂ H ₂ O ₄
268935	2-indanyl	oxalate	C ₂₁ H ₂₄ N ₂ O ₂ ·C ₂ H ₂ O ₄

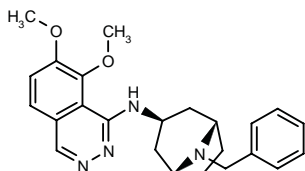
SOURCE – Lundbeck.

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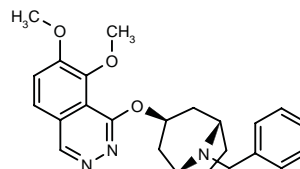
F-12342**267811**

exo-8-Benzyl-3-(7,8-dimethoxyphthalazin-1-ylamino)-8-azabicyclo[3.2.1]octane



C24 H28 N4 O2; Mol wt: 404.5112

ACTION – Potential antipsychotic agent with high affinity for dopamine D₂ receptors (pK_i = 10.08) and moderate affinity for 5-HT₂ and 5-HT_{1A} receptors (pK_i = 7.24 and 8.10, respectively); it possesses potent antipsychotic-like effects, as demonstrated by inhibition of methylphenidate-induced stereotyped gnawing in rats (ED₅₀ = 0.08 mg/kg i.p.), and a lack of side effects typical of conventional antipsychotics such as ataxia and flat body posture (> 40 mg/kg i.p.). Another phthalazine derivative with a similar pharmacological profile is:



F-12985 [267812]: C24 H27 N3 O3

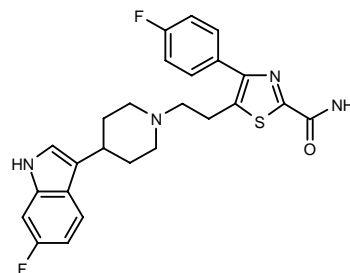
SOURCE – Pierre Fabre.

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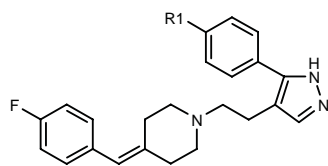
NRA-0562^{1,3,4}**267499**

5-[2-[4-(6-Fluoro-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-4-(4-fluorophenyl)thiazole-2-carboxamide

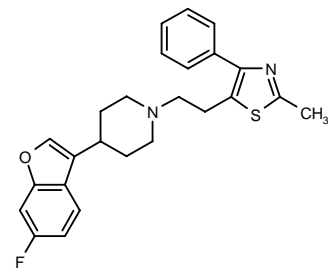


C25 H24 F2 N4 O S; Mol wt: 466.5536

ACTION – Potential antipsychotic agent with high affinity for dopamine D₄ (IC₅₀ = 1.79 nM for human receptor) and 5-HT_{2A} receptors (IC₅₀ = 1.25 nM for rat receptor) and α₁-adrenoceptors (IC₅₀ = 0.40 nM for rat receptor), and moderate affinity for the dopamine D₂ receptor (IC₅₀ = 9.55 nM for rat receptor). *In vivo* in rat brain, the compound showed greater occupancy of 5-HT_{2A} receptors in frontal cortex compared to D₂ receptors in striatum. It also potently inhibited methamphetamine-induced locomotor hyperactivity in mice (ED₅₀ = 1 mg/kg or less), with lower activity against methamphetamine-induced stereotypy (ED₅₀ = 1-10 mg/kg) and spontaneous locomotor activity in mice (ED₅₀ = 1-10 mg/kg) and for inducing catalepsy in rats (ED₅₀ = 1-10 mg/kg). Other related benzylidenepiperidine and arylpiperidine derivatives with a similar profile of activity are:



Compound	R1	Formula
NRA-0161 [265660]^{1,2,4}	F	C ₂₃ H ₂₃ F ₂ N ₃
NRA-0219 [267501]^{2,4}	H	C ₂₃ H ₂₄ FN ₃



NRA-0544 [267500]^{1,3,4}: C₂₅ H₂₅ F N₂ OS

SOURCES – Nihon Nohyaku; Taisho.

REFERENCES

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2. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.;Nihon Nohyaku Co., Ltd.) *Aromatic heterocyclic derivs.* JP 98095779.

3. Nakazato, A. et al. *Dopamine D4 receptor antagonists: Benzylidene piperidine and aryl piperidine derivatives.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-12.

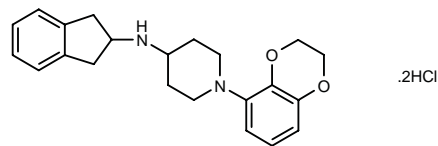
4. Nakazato, A. et al. *Dopamine D₂ receptor antagonists (4): Benzylidenepiperidine and arylpiperidine derivatives.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 126.

¹Identified compound **265660** (see **264340**) Drug Data Report 1998, 020(07): 0570.

ANTIDEPRESSANTS

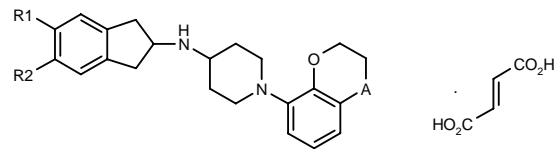
268202

N-[1-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperidin-4-yl]-*N*-(2-indanyl)amine dihydrochloride



C₂₂ H₂₆ N₂ O₂ . 2 HCl; Mol wt: 423.3812

ACTION – Agent for the treatment of depression, anxiety, obsessive–compulsive disorders, cognitive disorders, schizophrenia, sleep disorders and obesity with selective affinity for 5-HT_{1B} receptors relative to 5-HT_{1A} receptors. *In vivo*, compound was found to antagonize hypothermia induced by the 5-HT_{1B} agonist GR-46611 in guinea pigs following i.p. administration. Other specifically claimed compounds from this series of 2-aminoindane derivatives include the following:



Compound	R1	R2	A	Formula
268203	-OCH ₂ O-		O	C ₂₃ H ₂₆ N ₂ O ₄ .C ₄ H ₄ O ₄
268204	F	H	O	C ₂₂ H ₂₅ FN ₂ O ₂ .C ₄ H ₄ O ₄
268205	H	H	CH ₂	C ₂₃ H ₂₆ N ₂ O ₄ .C ₄ H ₄ O ₄
268206	OH	H	O	C ₂₂ H ₂₆ N ₂ O ₃ .C ₄ H ₄ O ₄

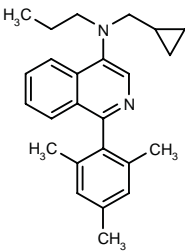
SOURCE – ADIR.

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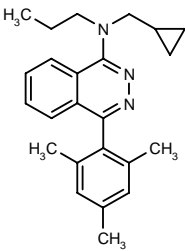
268250

N-(Cyclopropylmethyl)-*N*-propyl-*N*-[1-(2,4,6-trimethylphenyl)isoquinolin-4-yl]amine



C₂₅ H₃₀ N₂; Mol wt: 358.5260

ACTION – Agent for the treatment of stress-related disorders such as depression and anxiety that exerts its action via an interaction with corticotropin-releasing factor (CRF₁) receptors. Another representative compound within this series of isoquinolinamine and phthalazinamine derivatives having agonist or antagonist activity at human CRF₁ receptors is:



268251: C₂₄ H₂₉ N₃

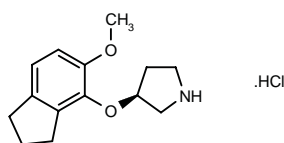
SOURCE – Neurogen.

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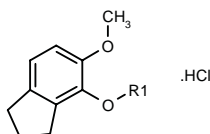
268591

(+)-(S)-3-(5-Methoxyindan-4-yloxy)pyrrolidine hydrochloride



C₁₄ H₁₉ N O₂ . HCl; Mol wt: 269.7700

ACTION – Agent for the treatment of CNS disorders such as depression, anxiety, obsessive–compulsive disorders, panic attacks, agoraphobia, eating disorders, urinary incontinence, impotence, aggression and drug abuse, a potent 5-HT_{2C} agonist with selectivity over 5-HT_{2A} receptors, as demonstrated *in vitro* in a binding assay (pK_i = 8 and 6.8, respectively). Agonist activity was demonstrated *in vivo* in the penile erection test in rats, where it displayed a minimum effective dose (MED) of 0.46 mg/kg. Antidepressant activity was demonstrated in the DRL-72 test in rats (MED = 3 mg/kg). Within this series of azetidine and pyrrolidine derivatives, the following compounds are also included:



Compound	R1	Isomer	Formula
268592	3-pyrrolidinyl	racemic	C ₁₄ H ₁₉ NO ₂ .HCl
268593	3-azetidinyl		C ₁₃ H ₁₇ NO ₂ .HCl

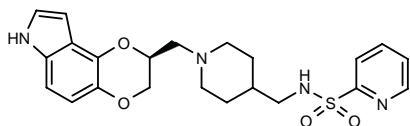
SOURCE – Akzo Nobel.

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268684

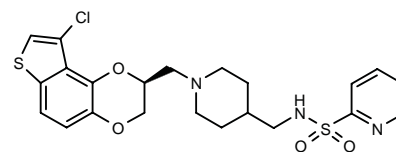
(S)-N-[1-(2,3-Dihydro-7H-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)piperidin-4-ylmethyl]pyridine-2-sulfonamide



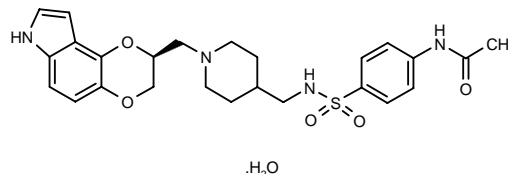
C₂₂ H₂₆ N₄ O₄ S; Mol wt: 442.5374

ACTION – Agent for the treatment of CNS disorders such as depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, Tourette's syndrome, sexual dysfunction, drug addiction, Alzheimer's disease, panic attacks and eating disorders, as well as obesity, cardiovascular and cerebrovascular disorders and diabetes, with high affinity for 5-HT_{1A} (99% inhibition of [³H]-8-OH-DPAT binding in rat hippocampal preparations at 1 μM) and D₂-like receptors (105% inhibition of [³H]-(S)-sulpiride binding in rat brain striatal preparations at 1 μM). A representative compound from a series of hetero-

arylsulfonamide derivatives, wherein the following are also included:



268685: C₂₂ H₂₄ Cl N₃ O₄ S₂



268686: C₂₅ H₃₀ N₄ O₅ S . H₂ O

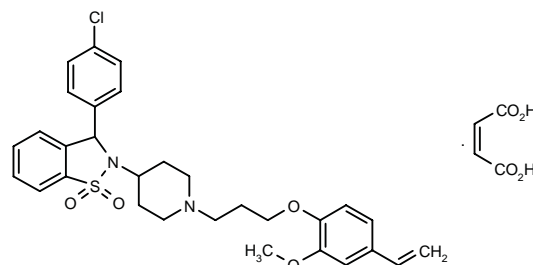
SOURCE – Knoll.

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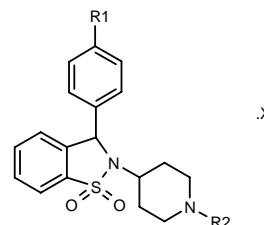
268698

3-(4-Chlorophenyl)-2-[1-[3-(2-methoxy-4-vinylphenoxy)propyl]piperidin-4-yl]-2,3-dihydrobenzo[d]-isothiazol S,S-dioxide maleate



C₃₀ H₃₃ Cl N₂ O₄ S . C₄ H₄ O₄; Mol wt: 669.1913

ACTION – Modulator of neurotransmitter function, as demonstrated by its ability to block norepinephrine, 5-HT and dopamine uptake in rat whole brain synaptosomes (55.23, 48.78 and 67.94% inhibition, respectively, at 3.16 μM). Claimed for the treatment of depression and Parkinson's disease. Within this series of 2,3-dihydrobenzo[d]isothiazoles, the following are also included:



Compound	R1	R2	X	Formula
268699	Cl	1,3-dioxo-2-iso-indoliny-(CH ₂) ₃	maleate	C ₂₉ H ₂₈ ClN ₃ O ₄ S.C ₄ H ₄ O ₄
268700	Cl	vinyl	maleate	C ₂₀ H ₂₁ ClN ₂ O ₂ S.C ₄ H ₄ O ₄
268701	F	H	HCl	C ₁₈ H ₁₉ FN ₂ O ₂ S.HCl

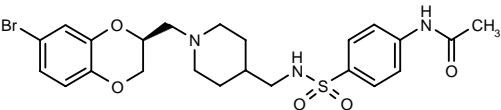
SOURCE – Hoechst Marion Roussel.

REFERENCES

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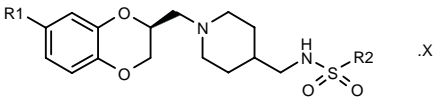
268716

(-)-(S)-4-Acetamido-N-[1-(7-bromo-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)piperidin-4-ylmethyl]benzene-sulfonamide

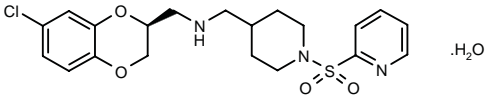


C23 H28 Br N3 O5 S; Mol wt: 538.4602

ACTION – Agent for the treatment of CNS disorders such as depression, anxiety, psychoses, tardive dyskinesia, Parkinson’s disease, Tourette’s syndrome, sexual dysfunction, drug addiction, Alzheimer’s disease, panic attacks and eating disorders, as well as obesity, cardiovascular and cerebrovascular disorders and diabetes, with potent affinity for 5-HT_{1A} and dopamine D₂-like (D₂, D₃ and D₄) receptors (K_i = 14 and 23 nM, respectively). A representative compound from a series of sulfonamide derivatives, wherein the following are also included:



Compound	R1	R2	X	Formula
268718	Cl	3-Pyr	H2O	C ₂₀ H ₂₄ ClN ₃ O ₄ S .H ₂ O
268719	Cl	3,4-(MeO)2-Ph		C ₂₃ H ₂₉ ClN ₃ O ₆ S
268720	Cl	2,4-(F)2-Ph		C ₂₁ H ₂₃ ClF ₂ N ₃ O ₄ S
268721	Cl	4-(AcNH)-Ph		C ₂₃ H ₂₈ ClN ₃ O ₅ S
268722	Cl	2,6-(F)2-Ph		C ₂₁ H ₂₃ ClF ₂ N ₃ O ₄ S
268723	CF3	2-Pyr		C ₂₁ H ₂₄ F ₃ N ₃ O ₄ S
268724	Cl	2,3-(Cl)-Ph		C ₂₁ H ₂₃ Cl ₃ N ₃ O ₄ S
268725	Br	2,4-(F)2-Ph		C ₂₁ H ₂₃ BrF ₂ N ₃ O ₄ S



268717: C20 H24 Cl N3 O4 S . H2 O

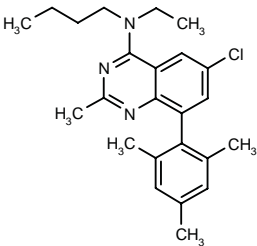
SOURCE – Knoll.

REFERENCES

1. Wishart, N. and Birch, A.M. (Knoll AG) *Sulfonamide cpds. having 5-HT receptor activity.* WO 9829411.

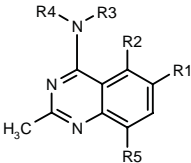
268830

4-(N-Butyl-N-ethylamino)-6-chloro-2-methyl-8-(2,4,6-trimethylphenyl)quinazoline

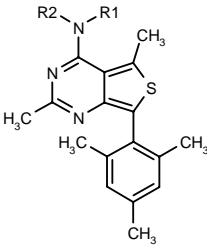


C24 H30 Cl N3; Mol wt: 395.9750

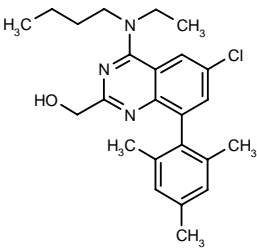
ACTION – Corticotropin-releasing factor (CRF₁) receptor antagonist with potential in the treatment of depression, eating disorders, Alzheimer’s disease, schizophrenia, Parkinson’s disease, Huntington’s chorea, amyotrophic lateral sclerosis, rheumatoid arthritis, pain, obesity, alcohol dependence, cardiovascular disorders and as an immunomodulator. A representative compound from a series of fused pyrimidine derivatives, wherein the following are also included:



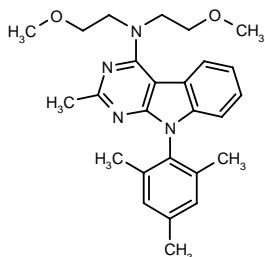
Compound	R1	R2	R3	R4	R5	Formula
268831	H	Me	CH2CH2-OMe	CH2CH2-OMe	2,4,6-(Me)3-Ph	C ₂₅ H ₃₃ N ₃ O ₂
268832	Cl	H	Et	Bu	2,4-(Me)2-Ph	C ₂₃ H ₂₆ ClN ₃
268833	Cl	H	-CH2CH2OCH2CH2-		2,4,6-(Me)3-Ph	C ₂₂ H ₂₄ ClN ₃ O
268834	Cl	H	Et	Bu	4-MeO-Ph	C ₂₂ H ₂₆ ClN ₃ O
268836	H	H	cyclopropyl-CH2	Pr	2,4,6-(Me)3-3-Pyr	C ₂₄ H ₃₀ N ₄



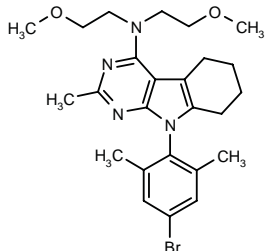
Compound	R1	R2	Formula
268835	CH2CH2OMe	CH2CH2OMe	C ₂₃ H ₃₁ N ₃ O ₂ S
268837	Pr	cyclopropyl-CH2	C ₂₄ H ₃₁ N ₃ S



268838: C24 H30 Cl N3 O



268839: C26 H32 N4 O2



268840: C25 H33 Br N4 O2

SOURCE – Yoshitomi.

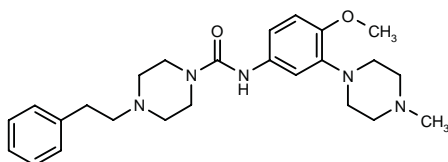
REFERENCES

1. Tanaka, H. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Fused pyrimidine cpds. and medicinal use thereof*. WO 9829397.

F-12682

267690

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4-(2-phenylethyl)piperazine-1-carboxamide



C25 H35 N5 O2; Mol wt: 437.5845

ACTION – Potent, high-efficacy and rapid-acting antidepressant with potent and selective inverse agonist activity at human 5-HT_{1B} and 5-HT_{1D} receptors (pK_i = 8.66) and no affinity for a number of other serotonergic and nonserotonergic receptors except 5-HT_{2A} receptors (pK_b = 7.30). Inverse agonist activity was demonstrated by inhibition of basal [³⁵S]-GTPγS binding to human recombinant 5-HT_{1B} and 5-HT_{1D} receptors. *In vivo*, F-12682 increased extracellular 5-HT levels in guinea pig frontal cortex following oral administration and it was effective as a centrally active 5-HT_{1B} antagonist in the social behavioral deficit paradigm in mice (ED_{50} = 0.10 mg/kg i.p., 0.11 mg/kg p.o.).

SOURCE – Pierre Fabre.

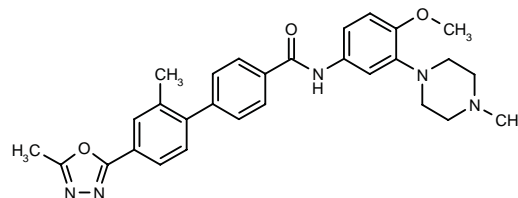
REFERENCES

1. Halazy, S. et al. (Pierre Fabre Médicament) *Novel aromatic piperazines derived from substd. cycloazanes, method for preparing same, pharmaceutical compsns., and use thereof as drugs*. WO 9728141.
2. Jorand-Lebrun, C. et al. *Synthesis and pharmacological studies of a new 5HT_{1B/1D} receptors inverse agonist*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.162.

GMC2-29*

198118

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carboxamide



C29 H31 N5 O3; Mol wt: 497.5959

ACTION – Potent and selective 5-HT_{1B/1D} receptor antagonist, as demonstrated in binding studies by IC₅₀ values for 5-HT_{1B} and 5-HT_{1D} receptors of 0.93 and 37 nM, respectively, versus values of 90 nM for 5-HT_{1A} receptors and > 1000 nM for inhibition of 5-HT reuptake; in functional studies, it inhibited sumatriptan-induced contractions of rabbit saphenous vein with a pA_2 value of 9.1. In an *in vivo* microdialysis experiment in rats, it potentiated the increase in 5-HT release in hippocampus induced by citalopram, and it prevented the 5-HT-mediated inhibition of acetylcholine release when given concomitantly with citalopram. It may be useful as an effective and/or rapid-onset antidepressant or for the treatment of obsessive-compulsive disorders, as well as for shortening the onset of antidepressant effect of selective 5-HT reuptake inhibitors (SSRIs).

SOURCES – Glaxo Wellcome; Merck KGaA.

REFERENCES

1. Oxford, A.W. et al. (Glaxo Wellcome plc) *Benzanilide derivs. as 5-HT_{1D} antagonists*. EP 533268, JP 94116251, US 5340810.
2. Liao, Y. et al. *Selective and potent 5-HT_{1B/1D} antagonists: Chemistry, modelling and pharmacological evaluation*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.100.

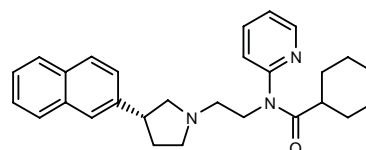
*Identified compound **198118** (see **194971**) Drug Data Report 1993, 015(08): 0707.

(+)-MCU-629*

267692

258661 (as oxalate)

(+)-*N*-[2-[3(*R*)-(2-Naphthyl)pyrrolidin-1-yl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide



C28 H33 N3 O; Mol wt: 427.5887

ACTION – One of the most active dual high-affinity 5-HT_{1A} receptor antagonists/5-HT reuptake inhibitors from a series of naphthalene derivatives, giving IC₅₀ values of 3.9 ± 1.2 and 36.7 ± 8.8 nM, respectively, versus > 1000 and > 100 nM, respectively, for 5-HT_{1D} and dopamine D₂ receptors. *In vivo*, it acted as a 5-HT_{1A} antagonist. Potentially useful in the treatment of depression.

SOURCE – Merck KGaA.

REFERENCES

1. März, J. et al. (Merck Patent GmbH) *Piperidines and pyrrolidines*. DE 19615232, WO 9740038.

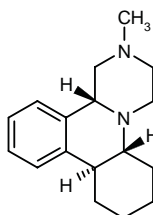
2. Sonesson, C. et al. *Naphthalene derivatives: A new class of high-affinity 5-HT_{1A} antagonists with 5-HT reuptake inhibitory activity*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.75.

*Identified compound **258661** (see **257728**) Drug Data Rep 1998, 020(02): 0116.

ORG-37415

267686

(±)-(5aα,9aβ,13bα)-2-Methyl-1,3,4,5a,6,7,8,9,9a,13b-decahydro-2H-pyrazino[1,2-f]phenanthridine



C17 H24 N2; Mol wt: 256.3906

ACTION – Potent, selective and orally active 5-HT_{2C} receptor antagonist ($pK_i = 6.7$ vs. 5.5 for 5-HT_{2A} receptors) with good chemical stability and no mutagenicity or photomutagenicity in the Ames test. Selected for further development as a potential antidepressant and anxiolytic.

SOURCE – Organon.

REFERENCES

1. Leysen, D. et al. *The role of radical formation in the optimisation process of 5-HT_{2C} antagonists as potential antidepressants and anxiolytics*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.227.

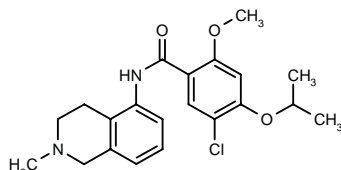
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

267521

261021 (as hydrochloride)*

5-Chloro-4-isopropoxy-2-methoxy-N-(2-methyl-1,2,3,4-tetrahydro-5-isoquinolyl)benzamide



C21 H25 Cl N2 O3; Mol wt: 388.8925

ACTION – Orally active anticonvulsant with high affinity for the [³H]-SB-204269-labeled binding site ($pK_i = 8.2$). Increases in seizure threshold in the maximal electroshock seizure (MES) test of 120% and 1130%, respectively, were noted in mice at 1 h and rats at 4 h following a dose of 10 mg/kg p.o. It exhibited a long duration of action, with significant activity for at least 6 h after dosing in rats.

SOURCE – SmithKline Beecham.

REFERENCES

1. Harling, J.D. et al. (SmithKline Beecham plc) *Substd. benzamide derivs. and their use as anticonvulsants*. WO 9748683.

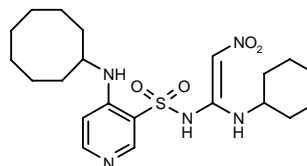
2. Harling, J.D. and Thompson, M. *Identification of a series of 1,2,3,4-tetrahydroisoquinolylbenzamides with potential anticonvulsant activity*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 099.

*See **260123** Drug Data Rep 1998, 020(04): 0296.

BM-401

267749

(E)-N-[1-(Cyclohexylamino)-2-nitrovinyl]-4-(cyclooctylamino)pyridine-3-sulfonamide



C21 H33 N5 O4 S; Mol wt: 451.5887

M.p 186-8 °C.

ACTION – Anticonvulsant with a profile comparable to that of phenytoin and BM-34, with good activity in the maximal electroshock seizure (MES) test in mice ($ED_{50} = 8.25$ mg/kg i.p.) and no activity against seizures induced by pentylenetetrazol, strychnine, bicuculline, picrotoxin or *N*-methyl-D,L-aspartate; it was less neurotoxic ($TD_{50} = 113.8$ mg/kg i.p.) than phenytoin ($TD_{50} = 65.5$ mg/kg i.p.) but more so than BM-34 ($TD_{50} = 147.2$ mg/kg i.p.), as evaluated in the rotarod test in mice, and it was devoid of diuretic activity in rats.

SOURCES – Université Catholique de Louvain, Louvain (BE); University of Namur, Namur (BE).

REFERENCES

1. Masereel, B. et al. *Design, synthesis and anticonvulsant activity of 1-(pyrid-3-ylsulfonamido)-2-nitroethylenes*. J Med Chem 1998, 41(7): 3239.

SOURCE – Merck KGaA.

REFERENCES

1. März, J. et al. (Merck Patent GmbH) *Piperidines and pyrrolidines*. DE 19615232, WO 9740038.

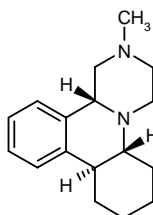
2. Sonesson, C. et al. *Naphthalene derivatives: A new class of high-affinity 5-HT_{1A} antagonists with 5-HT reuptake inhibitory activity*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abstr P.75.

*Identified compound **258661** (see **257728**) Drug Data Rep 1998, 020(02): 0116.

ORG-37415

267686

(±)-(5α,9α,13β)-2-Methyl-1,3,4,5a,6,7,8,9a,13b-decahydro-2H-pyrazino[1,2-f]phenanthridine



C17 H24 N2; Mol wt: 256.3906

ACTION – Potent, selective and orally active 5-HT_{2C} receptor antagonist ($pK_i = 6.7$ vs. 5.5 for 5-HT_{2A} receptors) with good chemical stability and no mutagenicity or photomutagenicity in the Ames test. Selected for further development as a potential antidepressant and anxiolytic.

SOURCE – Organon.

REFERENCES

1. Leysen, D. et al. *The role of radical formation in the optimisation process of 5-HT_{2C} antagonists as potential antidepressants and anxiolytics*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abstr P.227.

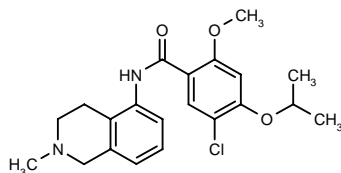
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

267521

261021 (as hydrochloride)*

5-Chloro-4-isopropoxy-2-methoxy-N-(2-methyl-1,2,3,4-tetrahydro-5-isoquinolyl)benzamide



C21 H25 Cl N2 O3; Mol wt: 388.8925

ACTION – Orally active anticonvulsant with high affinity for the [³H]-SB-204269-labeled binding site ($pK_i = 8.2$). Increases in seizure threshold in the maximal electroshock seizure (MES) test of 120% and 1130%, respectively, were noted in mice at 1 h and rats at 4 h following a dose of 10 mg/kg p.o. It exhibited a long duration of action, with significant activity for at least 6 h after dosing in rats.

SOURCE – SmithKline Beecham.

REFERENCES

1. Harling, J.D. et al. (SmithKline Beecham plc) *Substituted benzamide derivs. and their use as anticonvulsants*. WO 9748683.

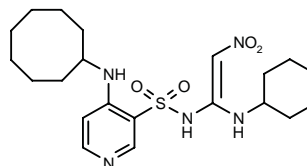
2. Harling, J.D. and Thompson, M. *Identification of a series of 1,2,3,4-tetrahydroisoquinolylbenzamides with potential anticonvulsant activity*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abstr MEDI 099.

*See **260123** Drug Data Rep 1998, 020(04): 0296.

BM-401

267749

(E)-N-[1-(Cyclohexylamino)-2-nitrovinyl]-4-(cyclooctylamino)pyridine-3-sulfonamide



C21 H33 N5 O4 S; Mol wt: 451.5887

M.p 186-8 °C.

ACTION – Anticonvulsant with a profile comparable to that of phenytoin and BM-34, with good activity in the maximal electroshock seizure (MES) test in mice ($ED_{50} = 8.25$ mg/kg i.p.) and no activity against seizures induced by pentylenetetrazol, strychnine, bicuculline, picrotoxin or *N*-methyl-D,L-aspartate; it was less neurotoxic ($TD_{50} = 113.8$ mg/kg i.p.) than phenytoin ($TD_{50} = 65.5$ mg/kg i.p.) but more so than BM-34 ($TD_{50} = 147.2$ mg/kg i.p.), as evaluated in the rotarod test in mice, and it was devoid of diuretic activity in rats.

SOURCES – Université Catholique de Louvain, Louvain (BE); University of Namur, Namur (BE).

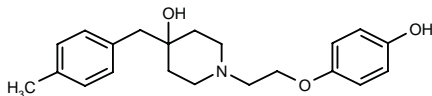
REFERENCES

1. Masereel, B. et al. *Design, synthesis and anticonvulsant activity of 1-(pyrid-3-ylsulfonamido)-2-nitroethylenes*. J Med Chem 1998, 41(7): 3239.

Co-101244

267522

1-[2-(4-Hydroxyphenoxy)ethyl]-4-(4-methylbenzyl)-piperidin-4-ol



C21 H27 N O3; Mol wt: 341.4483

ACTION – Potent subtype-selective NMDA receptor antagonist (SSNRA) with high affinity for NR1/2B (IC_{50} = 0.02 μ M) and much lower affinity for NR1/2A and NR1/2C receptor subtypes (IC_{50} = 250 and 230 μ M, respectively) and low affinity for α_1 -adrenoceptors (IC_{50} = 27 μ M). It exerted potent anticonvulsant activity in the maximal electroshock seizure (MES) test (ED_{50} = 1.5 mg/kg i.v.). Selected for further evaluation from a series of 4-benzyl-4-hydroxy-*N*-(hydroxyphenoxyalkyl)piperidines.

SOURCES – CoCensys; Warner-Lambert.

REFERENCES

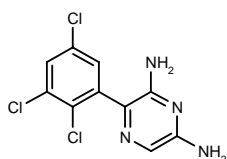
1. Cai, S.-X. et al. *Synthesis and SAR of 4-benzyl-4-hydroxy-*N*-(hydroxyphenoxyalkyl)piperidines as subtype selective NMDA receptor antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 114.

GW-273293X

251431

3-(2,3,5-Trichlorophenyl)pyrazine-2,6-diamine

GW-273293



C10 H7 Cl3 N4; Mol wt: 289.5523

ACTION – Sodium channel inhibitor with broad-spectrum anticonvulsant activity, a follow-up compound to lamotrigine. It was more potent than lamotrigine in the maximal electroshock seizure (MES) test (ED_{50} = 1.13 and 5.55 mg/kg i.p., respectively, and 2.49 and 6.13 mg/kg p.o., respectively) and against pentylenetetrazol-induced seizures (ED_{50} = 5.6 and 10 mg/kg i.p., respectively), and it also showed a higher therapeutic index (MES/ataxia) than lamotrigine (16.6 vs. 5.6). It has advanced to phase I clinical trials as a potential treatment for epilepsy and bipolar disorder.

SOURCE – Glaxo Wellcome.

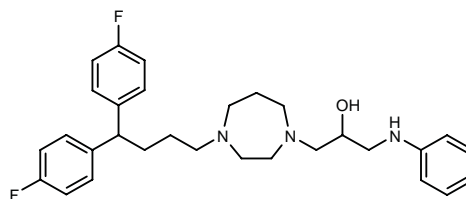
REFERENCES

1. Wild, D. et al. *Sodium channel inhibitors 3: GW273293X as a potential broad spectrum anticonvulsant*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.193.
2. *Glaxo Wellcome compounds in development*. Glaxo Wellcome plc Company Communication 1997, May 2.
3. *Glaxo Wellcome's R&D pipeline remains full and diverse*. Prous Science Daily Essentials 1998, Jan 21.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

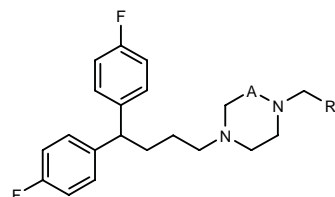
268386

1-[4-[4,4-Bis(4-fluorophenyl)butyl]perhydro-1,4-diazepin-1-yl]-3-(phenylamino)-2-propanol



C30 H37 F2 N3 O; Mol wt: 493.6383

ACTION – Dopamine reuptake inhibitor for the treatment of Parkinson's disease. Other exemplified compounds include the following:



Compound	A	R1	Formula
268387	-(CH2)2-	4-F-PhNHCH2CH(OH)	C ₃₀ H ₃₆ F ₃ N ₃ O
268388	-(CH2)2-	4-Me-PhNHCH2CH(OH)	C ₃₁ H ₃₉ F ₂ N ₃ O
268389	-(CH2)2-	4-OH-PhNHCH2CH(OH)	C ₃₀ H ₃₇ F ₂ N ₃ O ₂
268390	-(CH2)2-	CH(OH)CH2N(Me)Ph	C ₃₁ H ₃₉ F ₂ N ₃ O
268391	-(CH2)2-	CH(OAc)CH2NHPH	C ₃₂ H ₃₉ F ₂ N ₃ O ₂
268392	-(CH2)2-	CH2NHPH	C ₂₉ H ₃₅ F ₂ N ₃
268393	-(CH2)2-	CH2CH2NHPH	C ₃₀ H ₃₇ F ₂ N ₃
268394	-CH2-	CH2NHPH	C ₂₈ H ₃₃ F ₂ N ₃
268395	-CH2-	CH2CH2NHPH	C ₂₉ H ₃₅ F ₂ N ₃
268396	-(CH2)2-	CH(OMe)CH2NHPH	C ₃₁ H ₃₉ F ₂ N ₃ O

SOURCE – Pola Chemical.

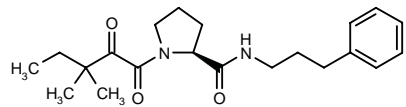
REFERENCES

1. Namiki, T. et al. (Pola Chemical Industries Inc.) *Inhibitors of dopamine reabsorption*. JP 98218866.

GPI-1337

267440

N-(3,3-dimethyl-2-oxopentanoyl)-L-proline 3-phenylpropyl amide



C21 H30 N2 O3; Mol wt: 358.4790

ACTION – Neuroimmunophilin with neurotrophic activity, a small-molecule FKBP12 (FK-506-binding protein) ligand ($K_i = 1.1 \mu\text{M}$ for inhibition of FKBP12 rotamase activity) with excellent oral bioavailability, good blood–brain barrier penetration and potent neuroregenerative effects in the MPTP model of Parkinson’s disease in mice; significant recovery of striatal innervation was observed in these animals at oral doses as low as 0.4 mg/kg compared to 4 mg/kg for GPI-1046.

SOURCE – Guilford.

REFERENCES

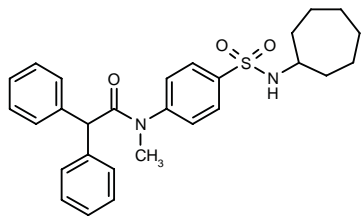
1. Hamilton, G.S. and Steiner, J.P. (Guilford Pharmaceuticals Inc.) *Small molecule inhibitors of rotamase enzyme activity*. CH 688775, EP 769006, JP 96333334, US 5614547, WO 9640633.

2. Wu, Y.-Q. et al. *N-Glyoxyl prolyl and pipercolyl amide FKBP12 ligands: Potent neurotrophic agents in an animal model of Parkinson's disease*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 103.

COGNITION-ENHANCING DRUGS

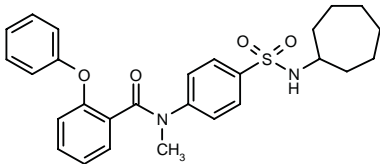
267755

N-[4-(*N*-Cycloheptylsulfamoyl)phenyl]-*N*-methyl-2,2-diphenylacetamide



C28 H32 N2 O3 S; Mol wt: 476.6378

ACTION – Neuroprotective agent that acts by blocking the activity of cytosolic phospholipase A_2 (cPLA₂) and the release of cytokines, e.g., IL-1 β and tumor necrosis factor (TNF- α), from neuronal cells. Potentially useful for the treatment of β -amyloid (A β)-related neurodegenerative disorders and Alzheimer’s disease. Another specifically claimed arylsulfonamide derivative is:



267756: C27 H30 N2 O4 S

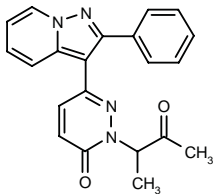
SOURCE – Athena Neurosciences.

REFERENCES

1. Varghese, J. et al. (Athena Neurosciences, Inc.) *Arylsulfonamides as phospholipase A_2 inhibitors*. WO 9825893.

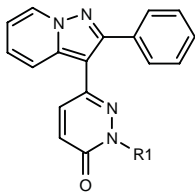
267904

2-(1-Methyl-2-oxopropyl)-6-(2-phenylpyrazolo[1,5-*a*]-pyridin-3-yl)pyridazin-3(2*H*)-one



C21 H18 N4 O2; Mol wt: 358.3992

ACTION – Adenosine A_1 receptor antagonist, as demonstrated in a binding study by more than 90% inhibition of [^3H]- N^6 -cyclohexyladenosine binding in rat brain membranes. Claimed for use in the treatment of cognition disorders and as an analgesic agent. Within this series of pyrazolopyridine derivatives, the following are also included:



Compound	R1	Formula
267905	CH2Ac	C ₂₀ H ₁₆ N ₄ O ₂
267906	t-BuCOCH2	C ₂₃ H ₂₂ N ₄ O ₂
267907	CH2COEt	C ₂₁ H ₁₈ N ₄ O ₂
267908	i-PrCH(Ac)	C ₂₃ H ₂₂ N ₄ O ₂
267909	i-BuCOCH2	C ₂₃ H ₂₂ N ₄ O ₂

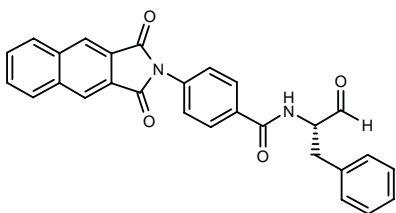
SOURCE – Fujisawa.

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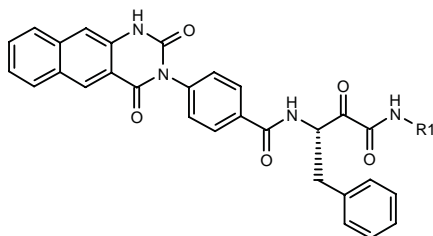
268167

N-[4-(1,3-Dioxo-2,3-dihydro-1*H*-benzo[*f*]isoindol-2-yl)-benzoyl]-*L*-phenylalaninal

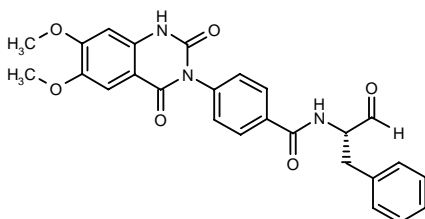


C₂₈H₂₀N₂O₄; Mol wt: 448.4760

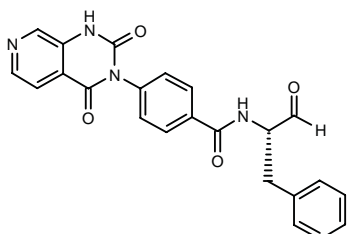
ACTION – An inhibitor of cysteine proteases such as calpain I and II and cathepsin B and L, with potential in the treatment of neurodegenerative disorders such as Alzheimer's disease and Huntington's disease, as well as epilepsy, cerebral, cardiac or renal ischemia, muscular dystrophy, coronary or cerebral vasospasm, cataracts, cancer, inflammation and restenosis following angioplasty. Other compounds from this series of substituted benzamide derivatives include the following:



Compound	R1	Formula
268169	H	C ₂₉ H ₂₂ N ₄ O ₅
268170	2-Pyr-CH ₂ CH ₂	C ₃₀ H ₂₀ N ₅ O ₅



268168: C₂₆H₂₃N₃O₆



268171: C₂₃H₁₈N₄O₄

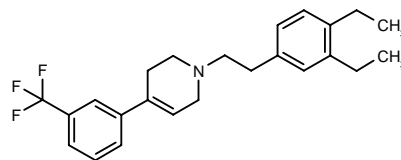
SOURCE – BASF.

REFERENCES

1. Lubisch, W. and Möller, A. (BASF AG) *Novel heterocyclically subst. benzamides and their use in fighting diseases*. WO 9825899.

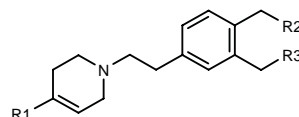
268183

1-[2-(3,4-Diethylphenyl)ethyl]-4-[3-(trifluoromethyl)-phenyl]-1,2,3,6-tetrahydropyridine



C₂₄H₂₈F₃N; Mol wt: 387.4862

ACTION – Neurotrophic and neuroprotective agent with potential in the treatment of a broad range of neurodegenerative disorders such as Alzheimer's disease and other types of dementia, memory disorders, Parkinson's disease, Huntington's chorea, neuropathies and amyotrophic lateral sclerosis. Within this series of specifically claimed 1-phenylalkyl-1,2,3,6-tetrahydropyridines, the following are also included:



Compound	R1	R2	R3	Formula
268184	3-CF ₃ -Ph	Bu	H	C ₂₆ H ₃₂ F ₃ N
268185	3-CF ₃ -Ph	H	Bu	C ₂₆ H ₃₂ F ₃ N
268186	6-Cl-2-Pyr	Me	Me	C ₂₂ H ₂₇ ClN ₂

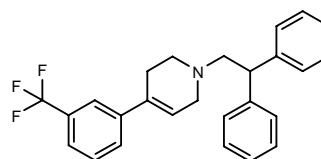
SOURCE – Sanofi.

REFERENCES

1. Baroni, M. et al. (Sanofi) *1-Phenylalkyl-1,2,3,6-tetrahydropyridines for treating Alzheimer's disease*. WO 9825903.

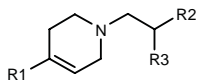
268187

1-(2,2-Diphenylethyl)-4-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridine



C₂₆H₂₄F₃N; Mol wt: 407.4766

ACTION – Neurotrophic and neuroprotective agent with potential in the treatment of a broad range of neurodegenerative disorders such as Alzheimer's disease and other types of dementia, memory disorders, Parkinson's disease, Huntington's chorea, neuropathies and amyotrophic lateral sclerosis. Within this series of specifically claimed 1-diphenylalkyl-1,2,3,6-tetrahydropyridines, the following are also included:



Compound	R1	R2	R3	Formula
268188	3-CF3-Ph	4-Cl-Ph	4-Cl-Ph	C ₂₆ H ₂₂ Cl ₂ F ₃ N
268189	3-CF3-Ph	3-CF3-Ph	3-CF3-Ph	C ₂₈ H ₂₂ F ₉ N
268190	3-CF3-Ph	4-MeO-Ph	4-MeO-Ph	C ₂₈ H ₂₈ F ₃ NO ₂
268191	3-CF3-Ph	Ph	4-F-Ph	C ₂₆ H ₂₃ F ₄ N
268192	3-CF3-Ph	H	CH(Ph) ₂	C ₂₇ H ₂₆ F ₃ N
268193	6-Cl-2-Pyr	4-Cl-Ph	4-Cl-Ph	C ₂₄ H ₂₁ Cl ₃ N ₂

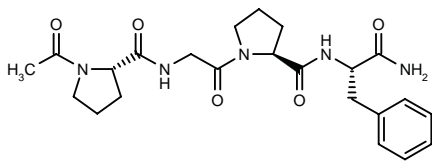
SOURCE – Sanofi.

REFERENCES

1. Baroni, M. et al. (Sanofi) *Diphenyl alkyl-tetrahydropyridines, process for their preparation, and pharmaceutical compsns. containing them.* WO 9825904.

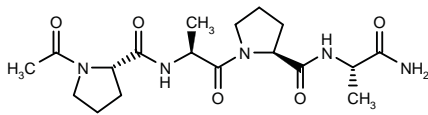
268254

Acetyl-L-prolyl-glycyl-L-prolyl-L-phenylalaninamide



C23 H31 N5 O5; Mol wt: 457.5279

ACTION – Neurotrophic agent with high affinity for cyclophilin-type immunophilins, a potent rotamase inhibitor shown to stimulate nerve growth factor (NGF)-induced neurite outgrowth in chick dorsal root ganglia, but reported to lack immunosuppressive activity. Potentially useful for the treatment of neurological disorders such as peripheral neuropathies and neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis. Another compound from this series of small-molecule peptidic inhibitors is:



268255: C18 H29 N5 O5

SOURCE – Guilford.

REFERENCES

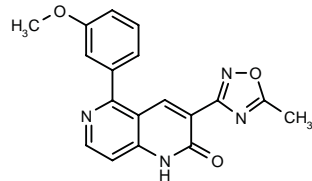
1. Hamilton, G.S. et al. (Guilford Pharmaceuticals Inc.) *Polyprolyl inhibitors of cyclophilin.* WO 9825950.

SX-3933

267806

5-(3-Methoxyphenyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1,6-naphthyridin-2(1H)-one

AC-3933



C18 H14 N4 O3; Mol wt: 334.3336

ACTION – Cognition-enhancing agent with high affinity for the benzodiazepine site on the GABA_A receptor (IC₅₀ = 2.21 nM) and inverse agonist activity at this receptor site. It was able to significantly improve scopolamine- and dizocilpine-induced memory deficits in mice on the object recognition test (ED₅₀ = 0.003-1 and 0.1-3 mg/kg p.o., respectively) and the Y-maze test (ED₅₀ = 0.3-3 and 0.1-10 mg/kg p.o., respectively), whereas it did not induce convulsions in mice at up to 100 mg/kg p.o. Acetylcholine release in rat hippocampus was significantly increased (298% compared to baseline) at a dose of 30 mg/kg p.o. It is suggested to have potential advantages over cholinergic transmission enhancers for the treatment of learning and memory disorders, including Alzheimer’s disease.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

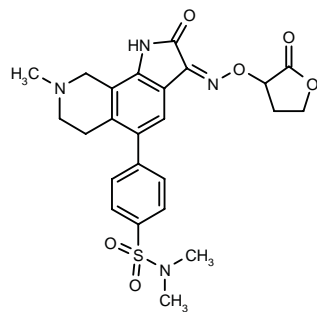
1. Masumoto, K. et al. *Structure-activity relationships and cognition-enhancing actions of novel 1,6-naphthyridine derivatives with benzodiazepine receptor inverse agonists activities.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 2-P-10.

2. Odai, O. et al. *Synthesis and pharmacological evaluation of novel 3-oxadiazolyl-1,6-naphthyridines as a new class of potential cognitive enhancers.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.256.

TREATMENT OF CEREBROVASCULAR DISEASES

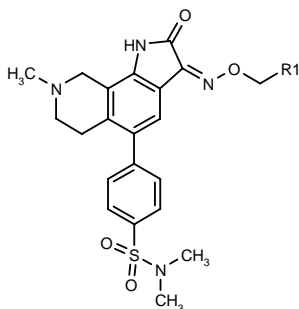
264412

N,N-Dimethyl-4-[8-methyl-2-oxo-3-(2-oxotetrahydrofuran-3-yloxyimino)-2,3,6,7,8,9-hexahydro-1H-pyrrolo[3,2-h]-isoquinolin-5-yl]benzenesulfonamide



C24 H26 N4 O6 S; Mol wt: 498.5574

ACTION – Excitatory amino acid receptor antagonist that displayed an IC_{50} value of 0.15 μ M for inhibition of [3H]-AMPA binding in rat cerebral cortex preparations. Potentially useful for the treatment of cerebrovascular disorders, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, schizophrenia, Parkinson's disease, epilepsy, anxiety, pain or drug addiction. Within this series of specifically claimed indole-2,3-dione-3-oxime derivatives, the following are also included:



Compound	R1	Formula
266715	4-Br-3-MeO-5-isoxazolyl	C ₂₅ H ₂₆ BrN ₅ O ₆ S
266716	4-Br-3-EtO-5-isoxazolyl	C ₂₆ H ₂₈ BrN ₅ O ₆ S
266717	2,5-(Me)2-3-oxo- -2,3-dihydro-4-isoxazolyl	C ₂₆ H ₂₉ N ₅ O ₆ S
266718	5-t-Bu-2-Me-3-oxo- -2,3-dihydro-4-isoxazolyl	C ₂₉ H ₃₅ N ₅ O ₆ S
266719	3-MeO-5-Me-4-isoxazolyl	C ₂₆ H ₂₉ N ₅ O ₆ S
266720	3-EtO-5-Me-4-isoxazolyl	C ₂₇ H ₃₁ N ₅ O ₆ S

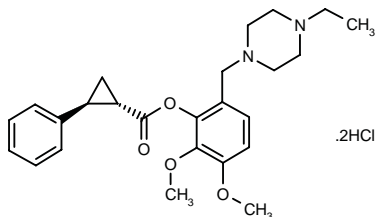
SOURCE – NeuroSearch.

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1. Wätjen, F. and Drejer, J. (NeuroSearch A/S) *Novel indole-2,3-dione-3-oxime derivs.* EP 869958, WO 9814447.

265434

2(*E*)-Phenylcyclopropane-1-carboxylic acid 6-(4-ethyl-piperazin-1-ylmethyl)-2,3-dimethoxyphenyl ester dihydrochloride



C₂₅ H₃₂ N₂ O₄ . 2 HCl; Mol wt: 497.4596

ACTION – Antiischemic agent capable of crossing the blood–brain barrier, proven to restore mitochondrial ATP synthesis and to increase the cytoprotective effect of trimetazidine in a myocardial ischemia–reperfusion model, as well as intracellular ATP content. Potentially useful for the treatment of acute cerebral, cardiac or peripheral ischemic disorders, neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as in the preservation of organs destined for transplantation.

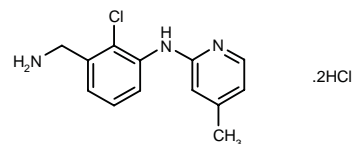
SOURCE – ADIR.

REFERENCES

1. Wierzbicki, M. et al. (ADIR et Cie.) *N-Benzylpiperazine derivs., process for their preparation and pharmaceutical compns. containing them.* EP 847999, JP 98175967, US 5849745.

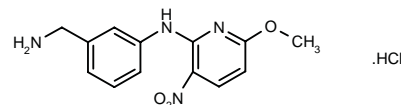
268847

N-[3-(Aminomethyl)-2-chlorophenyl]-*N*-(4-methyl-2-pyridyl)amine dihydrochloride



C₁₃ H₁₄ Cl N₃ . 2 HCl; Mol wt: 320.6494

ACTION – Nitric oxide synthase (NOS) inhibitor with selectivity for the neuronal isoform (nNOS; IC_{50} = 54.4 nM) over the inducible and endothelial isoforms (IC_{50} iNOS = 1774.9 nM; IC_{50} eNOS = 2882.4 nM), potentially useful for the treatment of cerebrovascular disorders. Another compound from this series of aromatic amines is:



268848: C₁₃ H₁₄ N₄ O₃ . HCl

SOURCE – Chugai.

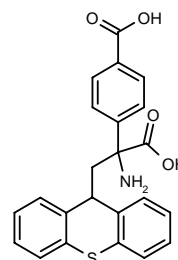
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1. Esaki, T. et al. (Chugai Pharmaceutical Co. Ltd.) *Aromatic amine derivs. having NOS inhibitory effect.* JP 98237028, WO 9828257.

LY-367366

267702

4-[1-Amino-1-carboxy-2-(9*H*-thioxanthen-9-yl)ethyl]-benzoic acid



C₂₃ H₁₉ N O₄ S; Mol wt: 405.4721

ACTION – Potent group 1 metabotropic glutamate receptor (mGluR1 and mGluR5) antagonist from a series of α -substituted phenylglycines, with IC_{50} values of 6 ± 3 and 4 ± 1 μ M, respectively, for mGluR1 α and mGluR5a receptors versus an IC_{50} value of 10 μ M or more for mGluR4 receptors (group 3); IC_{50} values for inhibition of quisqualate-induced phosphoinositide hydrolysis in AV-12 cells transfected with the human mGluR1 α and mGluR5a receptor were 6.6 ± 2.9 and 5.6 ± 2.7 μ M, respectively. The compound demonstrated neuroprotective activity, although it was generally less effective than the potent and selective mGluR1 α antagonist LY-367385.

SOURCE – Lilly.

REFERENCES

1. Clark, B.P. and Harris, J.R. (Eli Lilly and Company, Ltd.) *Pharmaceutical subst. propanoic acid derivs.* EP 849263.

2. Bruno, V. et al. *Neuroprotective activity of the group-I metabotropic glutamate receptor antagonists, LY367385 and LY367366.* Soc Neurosci Abst 1998, 24(Part 1): Abst 93.12.

3. Clark, B.P. et al. *α -Substituted phenylglycines as group 1 metabotropic glutamate receptor antagonists.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.183.

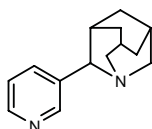
4. Thomas, N.K. et al. *Novel phenylglycines as metabotropic glutamate receptor antagonists.* Soc Neurosci Abst 1998, 24 (Part 1): Abst 229.15.

MISCELLANEOUS NEUROLOGIC DRUGS

RJR-2531

267503

2-(3-Pyridyl)-1-azatricyclo[3.3.1.1^{3,7}]decane



C14 H18 N2; Mol wt: 214.3102

ACTION – Potent nicotinic acetylcholine receptor (nAChR) antagonist that binds with high affinity to the $\alpha 4\beta 2$ -containing nAChRs ($K_i = 15$ nM) and appears to lack subtype specificity as regards ganglionic and neuromuscular nAChRs.

SOURCE – R.J. Reynolds Tobacco.

REFERENCES

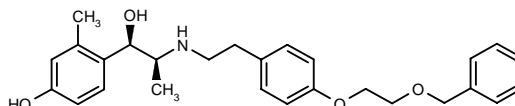
1. Bhatti, B.S. et al. *(2-(3-Pyridyl)-1-azatricyclo[3.3.1.1(3,7)]decane), RJR-2531, a potent antagonist at the nicotinic acetylcholine receptor.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 154.

RESPIRATORY DRUGS

ASTHMA THERAPY

265906

(1*R*,2*S*)-2-[2-[4-(2-Benzyloxyethoxy)phenyl]ethylamino]-1-(4-hydroxy-2-methylphenyl)-1-propanol



C27 H33 N O4; Mol wt: 435.5607

ACTION – Bronchodilating agent that acts by virtue of its β_2 -adrenoceptor-agonist activity, with negligible stimulating effects on β_1 -adrenoceptors. Compound increased spontaneous motor activity in isolated uterus from pregnant rats ($EC_{50} = 0.113$ nM; β_2 effect), whereas no influence on heart rate (β_1 effect) was observed in isolated guinea pig atria at this concentration. A representative compound within a series of 2-amino-1-(4-hydroxy-2-methylphenyl)propanol derivatives.

SOURCE – Kissei.

REFERENCES

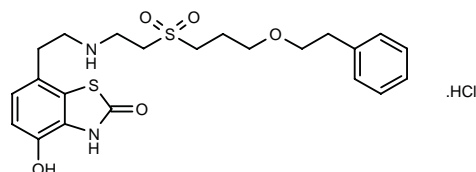
1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) *2-Amino-1-(4-hydroxy-2-methylphenyl)propanol derivs.* JP 98152460.

AR-C68397AA*

211502

4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propylsulfonyl]ethylamino]ethyl]benzothiazol-2(3*H*)-one hydrochloride

AR-C68397XX (free base)
FPL-68397



C22 H28 N2 O5 S2 . HCl; Mol wt: 501.0651

ACTION – Dual dopamine D_2 receptor and β_2 -adrenoceptor agonist ($A_{50} = 1.1$ and 11 nM, respectively; intrinsic activity = 0.90 and 0.69, respectively) expected to combine the beneficial effects of inhibition of afferent sensory nerve traffic (D_2 receptor) and antibronchoconstrictor effects (β_2 -adrenoceptor). It is currently in phase II clinical trials as a treatment for asthma and chronic obstructive pulmonary disease (COPD).

ACTION – Potent group 1 metabotropic glutamate receptor (mGluR1 and mGluR5) antagonist from a series of α -substituted phenylglycines, with IC_{50} values of 6 ± 3 and 4 ± 1 μ M, respectively, for mGluR1 α and mGluR5a receptors versus an IC_{50} value of 10 μ M or more for mGluR4 receptors (group 3); IC_{50} values for inhibition of quisqualate-induced phosphoinositide hydrolysis in AV-12 cells transfected with the human mGluR1 α and mGluR5a receptor were 6.6 ± 2.9 and 5.6 ± 2.7 μ M, respectively. The compound demonstrated neuroprotective activity, although it was generally less effective than the potent and selective mGluR1 α antagonist LY-367385.

SOURCE – Lilly.

REFERENCES

1. Clark, B.P. and Harris, J.R. (Eli Lilly and Company, Ltd.) *Pharmaceutical subst. propanoic acid derivs.* EP 849263.

2. Bruno, V. et al. *Neuroprotective activity of the group-I metabotropic glutamate receptor antagonists, LY367385 and LY367366.* Soc Neurosci Abst 1998, 24(Part 1): Abst 93.12.

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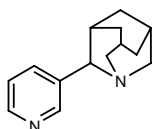
4. Thomas, N.K. et al. *Novel phenylglycines as metabotropic glutamate receptor antagonists.* Soc Neurosci Abst 1998, 24 (Part 1): Abst 229.15.

MISCELLANEOUS NEUROLOGIC DRUGS

RJR-2531

267503

2-(3-Pyridyl)-1-azatricyclo[3.3.1.1^{3,7}]decane



C14 H18 N2; Mol wt: 214.3102

ACTION – Potent nicotinic acetylcholine receptor (nAChR) antagonist that binds with high affinity to the $\alpha 4\beta 2$ -containing nAChRs ($K_i = 15$ nM) and appears to lack subtype specificity as regards ganglionic and neuromuscular nAChRs.

SOURCE – R.J. Reynolds Tobacco.

REFERENCES

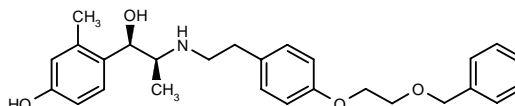
1. Bhatti, B.S. et al. *(2-(3-Pyridyl)-1-azatricyclo[3.3.1.1^{3,7}]decane), RJR-2531, a potent antagonist at the nicotinic acetylcholine receptor.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 154.

RESPIRATORY DRUGS

ASTHMA THERAPY

265906

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C27 H33 N O4; Mol wt: 435.5607

ACTION – Bronchodilating agent that acts by virtue of its β_2 -adrenoceptor-agonist activity, with negligible stimulating effects on β_1 -adrenoceptors. Compound increased spontaneous motor activity in isolated uterus from pregnant rats ($EC_{50} = 0.113$ nM; β_2 effect), whereas no influence on heart rate (β_1 effect) was observed in isolated guinea pig atria at this concentration. A representative compound within a series of 2-amino-1-(4-hydroxy-2-methylphenyl)propanol derivatives.

SOURCE – Kissei.

REFERENCES

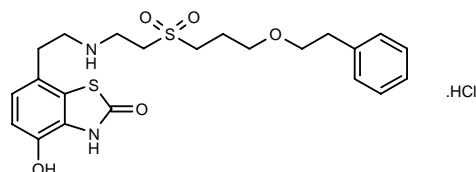
1. Kitazawa, M. et al. (Kissei Pharmaceutical Co., Ltd.) *2-Amino-1-(4-hydroxy-2-methylphenyl)propanol derivs.* JP 98152460.

AR-C68397AA*

211502

4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propylsulfonyl]ethylamino]ethyl]benzothiazol-2(3*H*)-one hydrochloride

AR-C68397XX (free base)
FPL-68397



C22 H28 N2 O5 S2 . HCl; Mol wt: 501.0651

ACTION – Dual dopamine D_2 receptor and β_2 -adrenoceptor agonist ($A_{50} = 1.1$ and 11 nM, respectively; intrinsic activity = 0.90 and 0.69, respectively) expected to combine the beneficial effects of inhibition of afferent sensory nerve traffic (D_2 receptor) and antibronchoconstrictor effects (β_2 -adrenoceptor). It is currently in phase II clinical trials as a treatment for asthma and chronic obstructive pulmonary disease (COPD).

SOURCE – Astra Charnwood.

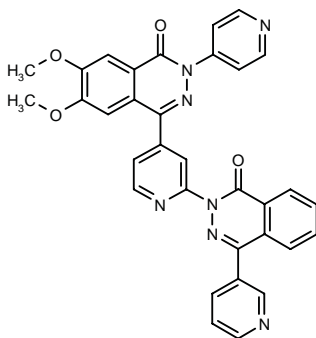
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2. Bonnert, R.V. et al. *Dual D₂-receptor and β₂-adrenoceptor agonists for the treatment of airways diseases*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.275.
3. Bonnert, R.V. et al. *Dual D₂-receptor and β₂-adrenoceptor agonists for the treatment of airways diseases*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.276.
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6. Gray, A.J. et al. *Disposition and metabolism of AR-C68397AA, a dual D₂-receptor and β₂-adrenoceptor agonist, in rat, dog and man*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.279.
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8. *Major innovations fuel R&D at Astra*. Prous Science Daily Essentials 1998, Jan 28.
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10. Fisons plc Annual Report 1994.

*Identified compound **211502** (see **205560**) Drug Data Report 1994, 016(09): 0811.

265435

6,7-Dimethoxy-2-(4-pyridyl)-4-[2-[1-oxo-4-(3-pyridyl)-1,2-dihydrophthalazin-2-yl]pyridin-4-yl]phthalazin-1(2H)-one



C33 H23 N7 O4; Mol wt: 581.5897

ACTION – Antiasthmatic agent with good antibronchoconstrictor and antiinflammatory properties, a selective phosphodiesterase type 4 (PDE4) inhibitor from a series of pyridine derivatives.

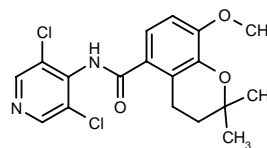
SOURCE – Tanabe.

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1. Ukita, T. et al. (Tanabe Seiyaku Co., Ltd.) *Pharmaceutical pyridine derivs., processes for preparing the same and intermediates therefor*. EP 848000, JP 98226685.

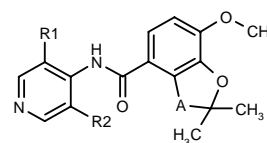
265901

N-(3,5-Dichloro-4-pyridyl)-8-methoxy-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-5-carboxamide



C18 H18 Cl2 N2 O3; Mol wt: 381.2572

ACTION – Antiinflammatory and bronchodilating agent, an inhibitor of phosphodiesterase type 4 (PDE4) from dog bronchial smooth muscle (92% inhibition at 0.1 mM). Also active *in vivo*, as demonstrated by the ability to inhibit bronchoconstriction elicited by ovalbumin in sensitized guinea pigs (69% inhibition at 10 mg/kg p.o.). Other representative oxygen-containing heterocyclic compounds include the following:



Compound	R1=R2	A	Formula
266697	Cl	-CH=CH-	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃
266698	Cl	-O-	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₄
266699	H	-O-	C ₁₆ H ₁₆ N ₂ O ₄

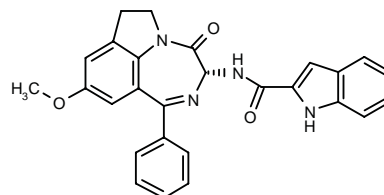
SOURCE – Kyowa Hakko.

REFERENCES

1. Nakazato, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Oxygen-containing heterocyclic cpds*. JP 98147585.

267519

(3R)-N-(9-Methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro[1,4]diazepino[6,7,1-h]indol-3-yl)-1H-indole-2-carboxamide



C27 H22 N4 O3; Mol wt: 450.4958

ACTION – The most promising candidate phosphodiesterase type 4 (PDE4) inhibitor from a series of methoxybenzodiazepine derivatives, giving an IC₅₀ of 0.65 for PDE4 compared to > 100 μM for PDE3, PDE1 and PDE5, with potential in the treatment of inflammatory disorders such as asthma.

SOURCE – Jouveinal.

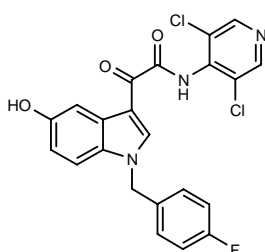
REFERENCES

1. Feru, F. et al. *Synthesis and structure-activity relationships of 9-methoxy-4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-h]indolines: Novel PDE 4 inhibitors.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 049.

AWD-12-281

267691

N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1*H*-indol-3-yl]-2-oxoacetamide



C22 H14 Cl2 F N3 O3; Mol wt: 458.2746

ACTION – Potent and selective inhibitor of phosphodiesterase type 4 (PDE4; IC_{50} = 7 nmol/l vs. > 1000 nmol/l for other PDE isozymes and 104 nmol/l for [3H]-rolipram binding) discovered using structure-based drug design, with antiinflammatory properties, high metabolic stability and reduced emetic potential.

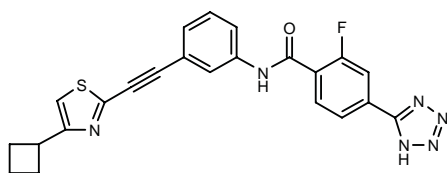
SOURCE – Asta Medica.

REFERENCES

1. Höfgen, N. et al. *Structure based drug design of a new type of selective PDE₄ inhibitors.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98.

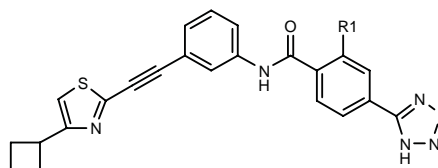
268157

N-[3-[2-(4-Cyclobutylthiazol-2-yl)ethynyl]phenyl]-2-fluoro-4-(1*H*-tetrazol-5-yl)benzamide



C23 H17 F N6 O S; Mol wt: 444.4923

ACTION – Antiallergic agent, a potent LTD₄ antagonist, as demonstrated *in vitro* by inhibition of LTD₄-induced guinea pig ileum contractions (IC_{50} = 0.57 nM), that also inhibits antigen-induced histamine release from rat peritoneal exudate cells (IC_{50} = 9.3 nM). *In vivo*, it was found to inhibit LTD₄-induced bronchoconstriction in guinea pigs (ID_{50} = 0.4 mg/kg p.o.), as well as the passive cutaneous anaphylaxis (PCA) reaction in rats (ID_{50} = 3.8 mg/kg). No deaths were observed following administration of 250 mg/kg/day p.o. x 14 days to rats. A representative compound from a series of 2-ethynylthiazoles, wherein the following are also included:



Compound	R1	Formula
268158	Me	C ₂₄ H ₂₀ N ₆ OS
268159	OCF ₃	C ₂₄ H ₁₇ F ₃ N ₆ O ₂ S

SOURCE – Daiichi Pharmaceutical.

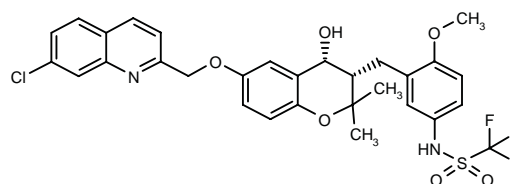
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1. Nakayama, A. et al. (Daiichi Pharmaceutical Co., Ltd.) *Ethynyl thiazole derivs.* JP 98195063.

CP-288886

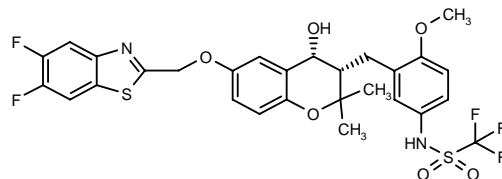
267517

(3*S*-*cis*)-*N*-[3-[6-(7-Chloroquinolin-2-ylmethoxy)-4-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-3-ylmethyl]-4-methoxyphenyl]trifluoromethanesulfonamide



C30 H28 Cl F3 N2 O6 S; Mol wt: 637.0722

ACTION – Potent LTD₄ (CysLT₁) receptor antagonist, as demonstrated in a binding assay (K_i = 0.004 μ M) and in a functional assay by inhibition of Ca²⁺ mobilization in U937 cells (IC_{50} = 0.0005 μ M). *In vivo*, it blocked antigen-induced airways obstruction in guinea pigs with an ED_{50} of 1.0 mg/kg p.o. at 1.0 h, showing comparable potency to zafirlukast, pranlukast and CP-195494. Rapid first-pass metabolism was noted following i.v. administration in rats, which may result in reduced buildup of potentially toxic hydroxylated metabolites. Following oral doses of 10 mg/kg, it was readily absorbed and showed high bioavailability, plasma levels being sustained for over 8 h at levels inhibiting Ca²⁺ influx in U937 cells. Another 2,2-dimethylchromanol compound with a similar profile is:



CP-265298 [267518]: C28 H25 F5 N2 O6 S2

SOURCE – Pfizer.

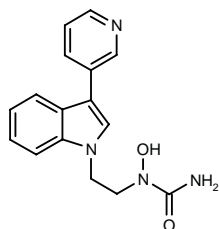
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1. Marfat, A. (Pfizer Inc.) *Sulfonamide derivs. of benzenefused hydroxy substd. cycloalkyl and heterocyclic ring cpds.* EP 665842, JP 95508534, US 5641789, WO 9408996.

2. Chambers, R.J. et al. *Development of 2,2-dimethylchromanol antagonists of leukotriene D₄.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 036.

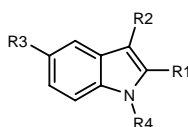
268825

N-Hydroxy-*N*-[2-[3-(3-pyridyl)indol-1-yl]ethyl]urea



C₁₆ H₁₆ N₄ O₂; Mol wt: 296.3284

ACTION – Antiallergic and antiinflammatory agent, a dual inhibitor of thromboxane synthase and 5-lipoxygenase, as demonstrated *in vitro* by inhibition of TxB₂ production in human platelet microsomes (IC₅₀ = 0.015 μM) and of LTB₄ production in rat polymorphonuclear leukocytes (IC₅₀ = 0.3 μM). In an *ex vivo* assay in rats, compound inhibited TxB₂ and LTB₄ production with ED₅₀ values of 3 and 3 mg/kg p.o., respectively. *In vivo*, it inhibited ovalbumin-induced bronchoconstriction in guinea pigs with an ED₅₀ value of 30 mg/kg p.o. Other compounds from this series of *N*-hydroxyurea derivatives include the following:



Compound	R1	R2	R3	R4	Formula
268826	H	CH ₂ N(OH)-CONH ₂	H	3-Pyr-CH ₂	C ₁₆ H ₁₆ N ₄ O ₂
268827	H	H	CH ₂ N(OH)-CONH ₂	3-Pyr-CH ₂	C ₁₆ H ₁₆ N ₄ O ₂
268828	3-Pyr	Me	CH ₂ N(OH)-CONH ₂	Me	C ₁₇ H ₁₈ N ₄ O ₂
268829	H	3-Pyr	CH ₂ N(OH)-CONH ₂	Me	C ₁₆ H ₁₆ N ₄ O ₂

SOURCE – Nikken Chemicals.

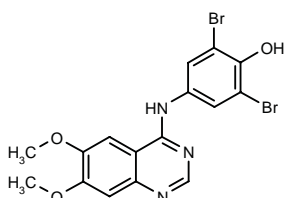
REFERENCES

1. Takano, M. et al. (Nikken Chemicals Co., Ltd.) *N*-Hydroxyurea derivs. and medicinal compns. containing the same. JP 98237066, JP 98237067, JP 98237068, WO 9829408.

WHI-P97

267510

2,6-Dibromo-4-(6,7-dimethoxyquinazolinyl-4-ylamino)-phenol



C₁₆ H₁₃ Br₂ N₃ O₃; Mol wt: 455.1047

ACTION – Potential antiasthmatic and antiallergic agent that inhibits IgE/antigen-induced LTC₄ and LTB₄ release from mast cells in a concentration-dependent fashion and appears to inhibit leukotriene synthesis by inhibiting the translocation of 5-lipoxygenase from cytosol to membrane.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

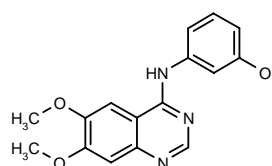
REFERENCES

1. Malaviya, R. et al. *Inhibition of 5-lipoxygenase translocation by halogenated-methoxy quinazoline derivative in mast cells*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 363.

WHI-P180

267509

3-(6,7-Dimethoxyquinazolin-4-ylamino)phenol



C₁₆ H₁₅ N₃ O₃; Mol wt: 297.3125

ACTION – Antiallergic agent shown to inhibit IgE/antigen-induced histamine, LTC₄ and tumor necrosis factor-α (TNF-α) release from mast cells in a concentration-dependent manner and to prevent immune complex-mediated systemic anaphylactic shock in mice. Potentially useful for the prophylaxis of allergic rhinitis, urticaria and food allergy.

SOURCES – Wayne Hughes Institute, St. Paul, MN (US); Zeneca.

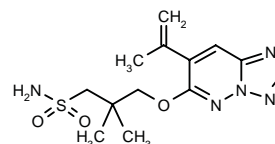
REFERENCES

1. Barker, A.J. (Zeneca Ltd.) *Quinazoline derivs*. CA 2086968, EP 566226, JP 94073025, US 5616582.

2. Malaviya, R. et al. *Modulation of mast cell mediated allergic reactions by a novel dimethoxy-quinazoline derivative*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 364.

267965

3-(7-Isopropenyl-1,2,4-triazolo[1,5-*b*]pyridazin-6-yloxy)-2,2-dimethylpropanesulfonamide



C₁₃ H₁₉ N₅ O₃ S; Mol wt: 325.3911

ACTION – Antiallergic and antiinflammatory agent with PAF-antagonist and eosinophil chemotaxis-inhibitory activity. A representative compound from a series of condensed pyridazine derivatives.

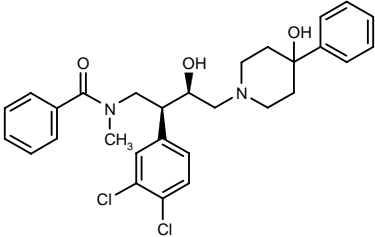
SOURCE – Takeda.

REFERENCES

1. Kawano, Y. and Ashida, Y. (Takeda Chemical Industries, Ltd.) *Condensed pyridazine derivs., their preparation method and their agents.* JP 98204087.

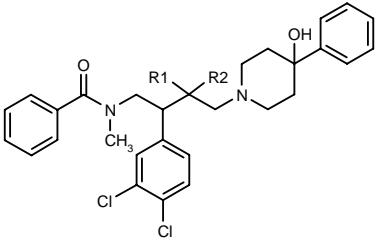
267368

N-[2(S)-(3,4-Dichlorophenyl)-3(R)-hydroxy-4-(4-hydroxy-4-phenylpiperidin-1-yl)butyl]-N-methylbenzamide

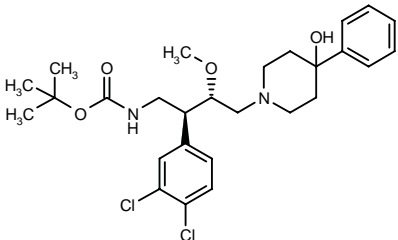


C29 H32 Cl2 N2 O3; Mol wt: 527.4888

ACTION – Antiasthmatic and antiinflammatory agent, a dual neurokinin NK₁ and NK₂ receptor antagonist, as demonstrated in binding assays by 81.0 and 88.0% inhibition, respectively, of [³H]-substance P and [³H]-neurokinin A binding in CHO cells transfected with human NK₁ and NK₂ receptors at a concentration of 1 μM. Within this series of substituted arylalkylamines, the following are also included:



Compound	R1	R2	Isomer	Formula
267370	-O-			C ₂₉ H ₃₀ Cl ₂ N ₂ O ₃
267371	-N(OMe)-			C ₃₀ H ₃₃ Cl ₂ N ₃ O ₃
267372	3,5-(CF ₃) ₂ - -PhCH ₂ O	H	2S,3S	C ₃₈ H ₃₆ Cl ₂ F ₆ N ₂ O ₃



267369: C27 H36 Cl2 N2 O4

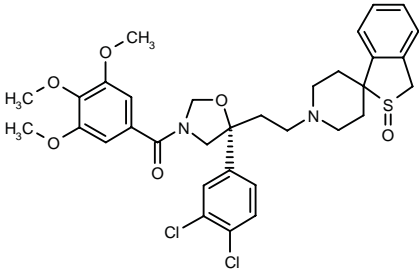
SOURCE – Schering-Plough.

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1. Reichard, G.A. and Aslanian, R.G. (Schering Corp.) *Subst. arylalkylamines as neurokinin antagonists.* US 5789422.

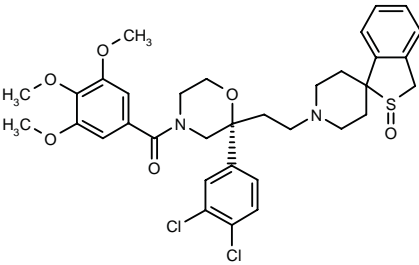
267886

1'-[2-[5(R)-(3,4-Dichlorophenyl)-4-(3,4,5-trimethoxybenzoyl)oxazolidin-5-yl]ethyl]spiro[benzo[c]thiophen-1(3H)-4'-piperidine] S-oxide



C33 H36 Cl2 N2 O6 S; Mol wt: 659.6274

ACTION – Potent neurokinin NK₁ and NK₂ receptor antagonist (IC₅₀ = 5.9 and 0.85 ng/ml, respectively, in binding assays) proven to potently inhibit [Nle¹⁰]-NKA(4-10)-induced bronchoconstriction in guinea pigs (ID₅₀ = 0.074 mg/kg i.v.) and the substance P-induced increase in vascular permeability in guinea pig trachea (ID₅₀ = 0.025 mg/kg i.v.). Another compound from this series of optically active sulfoxide derivatives is:



267887: C34 H38 Cl2 N2 O6 S

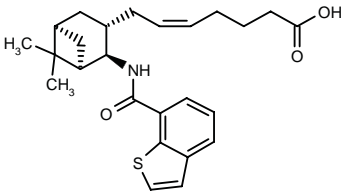
SOURCE – Sankyo.

REFERENCES

1. Nishi, T. et al. (Sankyo Co., Ltd.) *Optically active sulfoxide derivs.* JP 98182649, JP 98182650.

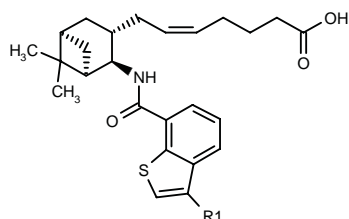
268081

(1R,2R,3S,5S)-7-[2-(Benzo[b]thien-7-ylcarboxamido)-6,6-dimethylbicyclo[3.1.1]heptan-3-yl]-5(Z)-heptenoic acid



C25 H31 N O3 S; Mol wt: 425.5899

ACTION – Antiallergic, antiasthmatic and antiinflammatory agent that acts as a PGD_2 (DP) receptor antagonist and inhibits eosinophil infiltration. DP receptor antagonism was evaluated in a binding assay using $[^3\text{H}]\text{-PGD}_2$ as the ligand and human platelet membranes as the source of receptor ($\text{IC}_{50} = 26 \text{ nM}$) and in a functional assay measuring inhibition of PGD_2 -stimulated cAMP production in human platelets ($\text{IC}_{50} = 42 \text{ nM}$). It inhibited nasal obstruction induced in guinea pigs by ovalbumin (80% inhibition at 10 mg/kg p.o.). Other representative compounds within this series of fused heterocyclic benzenecarboxylic acid amide derivatives include the following:



Compound	R1	Formula
268082	OMe	$\text{C}_{26}\text{H}_{33}\text{NO}_4\text{S}$
268083	Me	$\text{C}_{26}\text{H}_{33}\text{NO}_3\text{S}$
268084	Br	$\text{C}_{25}\text{H}_{30}\text{BrNO}_3\text{S}$

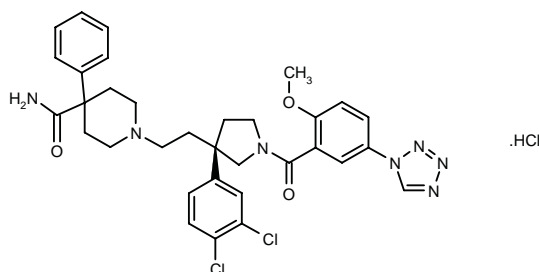
SOURCE – Shionogi.

REFERENCES

- Honma, T. et al. (Shionogi & Co. Ltd.) *Fused heterocyclic benzenecarboxylic acid amide derivs. and PGD_2 antagonists containing the same.* WO 9825915.

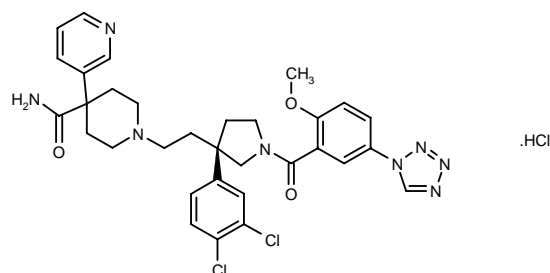
268638

1-[2-[3(R)-(3,4-Dichlorophenyl)-1-[2-methoxy-5-(1-tetrazolyl)benzoyl]pyrrolidin-3-yl]ethyl]-4-phenylpiperidine-4-carboxamide hydrochloride



$\text{C}_{33}\text{H}_{35}\text{Cl}_2\text{N}_7\text{O}_3 \cdot \text{HCl}$; Mol wt: 685.0524

ACTION – Tachykinin receptor antagonist with good activity against both NK_1 and NK_2 receptors ($\text{IC}_{50} = 2.79$ and 16.3 nM , respectively) and greatly improved metabolic stability compared to structurally related compounds. Potentially useful for the treatment of asthma, cough and bronchitis. Another specifically claimed compound from this series of pyrrolidine derivatives is:



268639: $\text{C}_{32}\text{H}_{34}\text{Cl}_2\text{N}_8\text{O}_3 \cdot \text{HCl}$

SOURCE – Hoechst Marion Roussel.

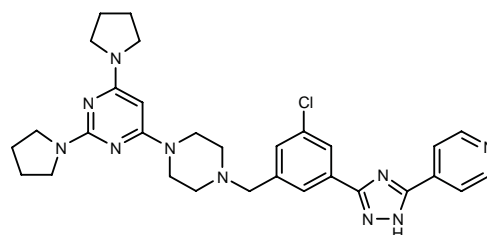
REFERENCES

- Burkholder, T.P. et al. (Hoechst Marion Roussel, Inc.) *Novel heterocyclic subst. pyrrolidine amide derivs.* WO 9827086.

VB-5122

267575

1-[2,6-Bis(1-pyrrolidinyl)pyrimidin-4-yl]-4-[3-chloro-5-[5-(4-pyridyl)-1H-1,2,4-triazol-3-yl]benzyl]piperazine



$\text{C}_{30}\text{H}_{35}\text{ClN}_{10}$; Mol wt: 571.1295

ACTION – Potent antioxidant ($\text{IC}_{50} = 5$ and $6 \mu\text{M}$, respectively, for inhibition of lipid peroxidation at 15 and 30 min) and highly potent inhibitor of the enzyme xanthine oxidase ($\text{IC}_{50} = 0.022 \mu\text{M}$) from a series prepared by combining lazaroids and 1,2,4-triazoles. It was also active in reducing xanthine oxidase activity in a model of asthma in which sensitized guinea pigs were challenged with ovalbumin.

SOURCE – Vrije Universiteit, Amsterdam (NL).

REFERENCES

- van der Goot, H. et al. *New antioxidants with strong free radical scavenging and xanthine oxidase inhibiting activity.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.243.

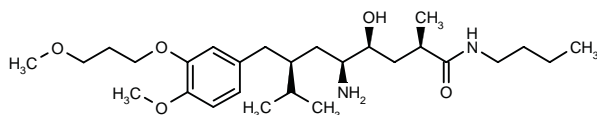
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

CGP-54061

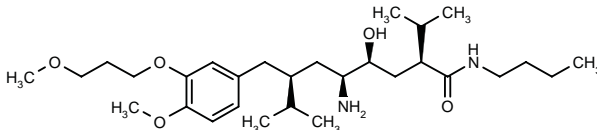
260287

(2*R*,4*S*,5*S*,7*S*)-5-Amino-*N*-butyl-4-hydroxy-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-2,8-dimethylnonanamide



C27 H48 N2 O5; Mol wt: 480.6852

ACTION – Potent, selective, orally active transition-state peptidomimetic inhibitor of renin (IC_{50} = 0.4, 3 and 4 nM, respectively, against purified human renin, human plasma renin and marmoset plasma renin) with good oral activity in sodium-depleted marmosets: it almost completely inhibited plasma renin activity over 24 h and produced a marked, long-lasting and dose-dependent reduction in mean arterial blood pressure following oral administration at doses of 1-10 mg/kg. Another related peptidomimetic renin inhibitor is:



260288: C29 H52 N2 O5

SOURCE – Novartis.

REFERENCES

1. Göschke, R. et al. (Ciba-Geigy AG) *δ*-Amino- γ -hydroxy- ω -aryl alkanolic acid amides with enzyme especially renin inhibiting activities. EP 678500, EP 678503, JP 96053434, JP 96081430, US 5559111, US 5627182, US 5646143.

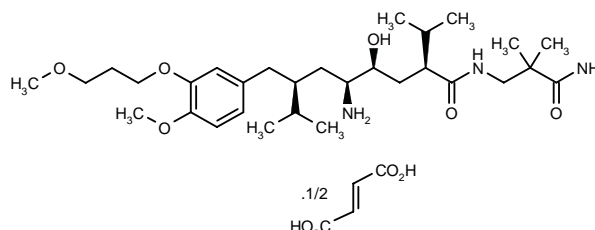
2. Goeschke, R. et al. Novel 2,7-dialkyl substituted 5(*S*)-amino-4(*S*)-hydroxy-8-phenyl-octanecarboxamide transition state peptidomimetics are potent and orally active inhibitors of human renin. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.229.

3. Rasetti, V. et al. Structure-based design and synthesis of novel potent and orally bioavailable peptidomimetic renin inhibitors. 1st Ital Swiss Meet Med Chem (Sept 23-26, Torino) 1997, 29.

CGP-60536B

267580

(2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide hemifumarate



C30 H53 N3 O6 . 1/2 C4 H4 O4; Mol wt: 609.7981

ACTION – Potent, selective, nonpeptide transition-state renin inhibitor (IC_{50} = 0.6, 0.6 and 2 nM, respectively, for inhibition of purified human renin, human plasma renin and marmoset plasma renin) with high enzyme specificity and some selectivity for primate renin (IC_{50} = 7-6500 nM, respectively, for dog, rabbit, rat and cat plasma renin). It proved to be one of the most potent orally active renin inhibitors in the salt-depleted marmoset model described to date, completely inhibiting plasma renin activity for up to 24 h at a dose of 3 mg/kg p.o. and providing pronounced, dose-dependent and sustained reductions in mean arterial pressure at doses of 1-10 mg/kg p.o. Selected for clinical trials.

SOURCE – Novartis.

REFERENCES

1. Göschke, R. et al. (Ciba-Geigy AG) *δ*-Amino- γ -hydroxy- ω -aryl alkanolic acid amides with enzyme especially renin inhibiting activities. EP 678500, EP 678503, JP 96053434, JP 96081430, US 5559111, US 5627182, US 5646143.

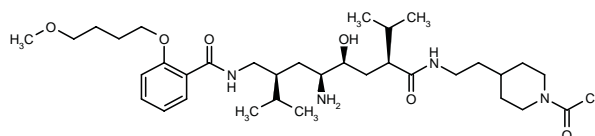
2. Maibaum, J. et al. Structural modification of the P2' position of 2,7-dialkyl substituted 5(*S*)-amino-4(*S*)-hydroxy-8-phenyl-octane-carboxamides: Discovery of a potent non-peptide renin inhibitor active after once daily dosing in marmosets. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.230.

CGP-62198A

267579

(2*S*,4*S*,5*S*,7*S*)-*N*-[7-[[2-(1-Acetyl-4-piperidiny)-ethyl]carbamoyl]-4-amino-5-hydroxy-2-isopropyl-8-methylnonyl]-2-(4-methoxybutoxy)benzamide

(2*S*,4*S*,5*S*,7*S*)-*N*-[2-(1-Acetyl-4-piperidin-4-yl)ethyl]-5-amino-4-hydroxy-2,7-diisopropyl-8-[2-(4-methoxybutoxy)benzamido]octanamide



C35 H60 N4 O6; Mol wt: 632.8810

ACTION – Highly potent and specific, nonpeptide transition-state renin inhibitor (IC_{50} = 0.6 and 0.3 nM, respectively, against purified human renin and human plasma renin) with species selectivity (IC_{50} = 40-2000 nM for dog, rabbit, guinea pig and rat plasma renin) and no activity against other human aspartyl proteases and HIV protease (IC_{50} > 10 μ M). The compound is one of the most potent orally active renin inhibitors in sodium-depleted marmosets reported to date, completely blocking plasma renin activity for almost 24 h at a dose of 3 mg/kg p.o. and providing a pronounced, dose-dependent and long-lasting reduction in mean arterial pressure after single oral doses of 1-10 mg/kg.

SOURCE – Novartis.

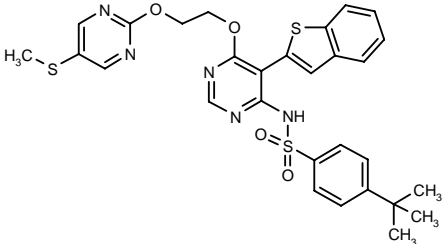
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2. Maibaum, J. et al. *Design and synthesis of novel, fully non-peptide transition state mimetic renin inhibitors bearing an O-alkyl substituted salicylamide (P3SP-P3)-moiety with high oral in vivo potency*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.231.

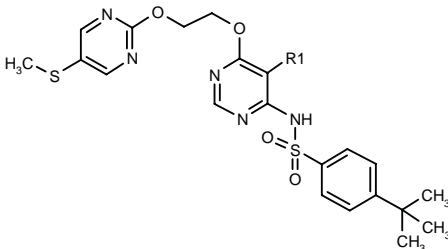
267874

N-[5-(Benzo[*b*]thien-2-yl)-6-[2-[5-(methylsulfanyl)pyrimidin-2-yloxy]ethoxy]pyrimidin-4-yl]-4-*tert*-butylbenzene-sulfonamide



C29 H29 N5 O4 S3; Mol wt: 607.7771

ACTION – Antihypertensive agent that acts through antagonism of endothelin (ET) receptors (IC_{50} = 0.026 nM against [125 I]-ET-1 binding in porcine arterial membrane preparations). Other particularly potent endothelin antagonists include the following:



Compound	R1	Formula
267876	2-Naph	C ₃₁ H ₃₁ N ₅ O ₄ S ₂
267877	2-thienyl	C ₂₅ H ₂₇ N ₅ O ₄ S ₃
267878	5-Me-2-thienyl	C ₂₆ H ₂₉ N ₅ O ₄ S ₃

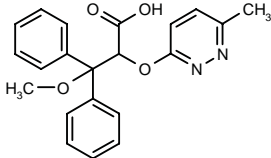
SOURCE – Tanabe.

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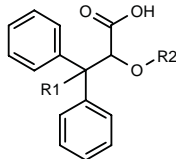
268247

3-Methoxy-2-(6-methylpyridazin-3-yloxy)-3,3-diphenyl-propionic acid



C21 H20 N2 O4; Mol wt: 364.3990

ACTION – Antihypertensive agent, an endothelin receptor antagonist from a series of heterocyclic carboxylic acid derivatives, wherein the following are also included:



Compound	R1	R2	Formula
268248	OMe	6-MeO-2-pyrazinyl-O	C ₂₁ H ₂₀ N ₂ O ₅
268249	Me	6-MeO-3-pyridazinyl-O	C ₂₁ H ₂₀ N ₂ O ₄

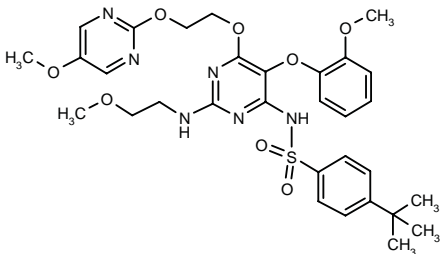
SOURCE – BASF.

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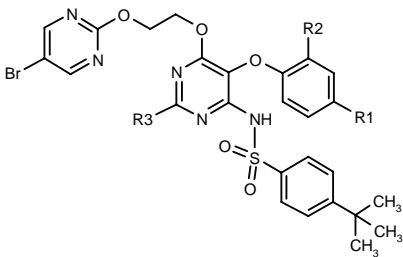
268562

4-*tert*-Butyl-*N*-[2-(2-methoxyethylamino)-5-(2-methoxyphenoxy)-6-[2-(5-methoxypyrimidin-2-yloxy)ethoxy]pyrimidin-4-yl]benzenesulfonamide



C31 H38 N6 O8 S; Mol wt: 654.7412

ACTION – Antihypertensive agent with endothelin receptor-antagonist activity (IC_{50} = 2.2 pM against [125 I]-ET-1 binding in porcine aortic membrane preparations). A representative compound from a series of benzene-sulfonamides, wherein the following are also included:



Compound	R1	R2	R3	Formula
268563	H	OMe	NHCH2CH2OH	C ₂₉ H ₃₃ BrN ₆ O ₇ S
268564	H	OMe	SCH2CH2OH	C ₂₉ H ₃₃ BrN ₆ O ₇ S ₂
268565	H	OMe	4-OH-1-Pip	C ₃₂ H ₃₇ BrN ₆ O ₇ S
268566	H	OMe	NHCH2CH2OMe	C ₃₀ H ₃₅ BrN ₆ O ₇ S
268567	Me	H	NHCH2CH2OH	C ₂₉ H ₃₃ BrN ₆ O ₆ S

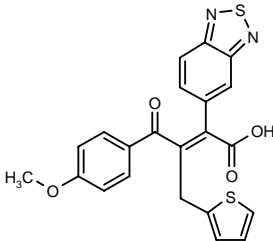
SOURCE – Tanabe.

REFERENCES

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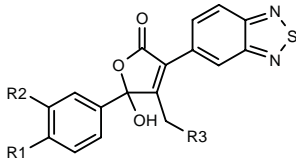
268628

2-(2,1,3-Benzothiadiazol-5-yl)-4-(4-methoxyphenyl)-4-oxo-3-(2-thienylmethyl)-2-butenic acid

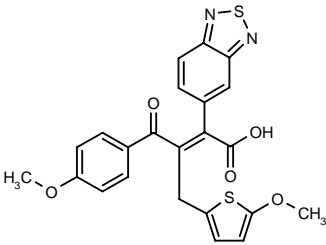


C22 H16 N2 O4 S2; Mol wt: 436.5104

ACTION – Endothelin receptor antagonist claimed for the treatment of hypertension, heart failure, renal insufficiency, cerebral infarction, renal, cerebral and myocardial ischemia, subarachnoid hemorrhage, inflammation, asthma and endotoxic shock. Other specifically claimed compounds from this series of 2,1,3-benzothia(oxa)diazole derivatives include the following:



Compound	R1	R2	R3	Formula
268630	OMe	H	2-furyl	C ₂₂ H ₁₆ N ₂ O ₅ S
268631	-O(CH2)3O-		3,4,5-(MeO)3-Ph	C ₂₉ H ₂₆ N ₂ O ₆ S
268632	-O(CH2)3O-		3,4-(i-PrO)2-5-MeO-Ph	C ₃₃ H ₃₄ N ₂ O ₆ S
268633	OMe	H	3-thienyl	C ₂₂ H ₁₆ N ₂ O ₄ S ₂



268629: C23 H18 N2 O5 S2

SOURCE – Merck KGaA.

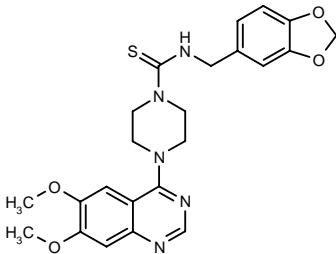
REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *2,1,3-Benzothia(oxa)diazole derivs. and their use as endothelin-receptor antagonists.* WO 9827077.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

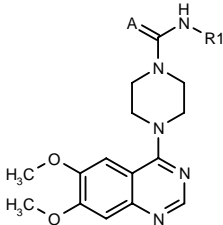
264407

N-(1,3-Benzodioxol-5-ylmethyl)-4-(6,7-dimethoxyquinazolin-4-yl)piperazine-1-carbothioamide

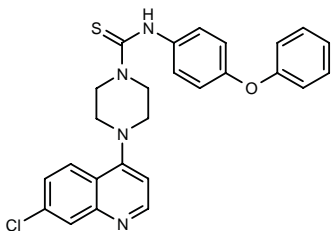


C23 H25 N5 O4 S; Mol wt: 467.5475

ACTION – Antiproliferative agent for the treatment of cancer, arteriosclerosis, restenosis and glomerulosclerosis, an inhibitor of platelet-derived growth factor (PDGF) receptor phosphorylation, as demonstrated in an *in vitro* assay using CHO cells expressing the PDGF receptor (IC₅₀ = 0.03 μM). It was active *in vivo* in inhibiting vascular intimal hypertrophy in rats at a dose of 30 mg/kg p.o., as well as in a proliferative glomerulonephritis model in rats. Other heterocyclic compounds include the following:



Compound	R1	A	Formula
266711	4-NO2-Ph	O	C ₂₁ H ₂₂ N ₆ O ₅
266712	3-Pyr-CH2	S	C ₂₁ H ₂₄ N ₆ O ₂ S
266714	4-CN-Ph	O	C ₂₂ H ₂₂ N ₆ O ₃



266713: C26 H23 Cl N4 OS

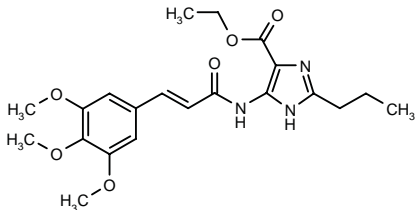
SOURCE – Kyowa Hakko.

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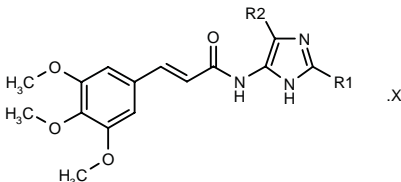
268032

2-Propyl-5(4)-(3,4,5-trimethoxycinnamoylamino)-imidazole-4(5)-carboxylic acid ethyl ester



C21 H27 N3 O6; Mol wt: 417.4593

ACTION – Inhibitor of vascular smooth muscle cell proliferation (IC₅₀ = 8 μM using thoracic aorta preparations from spontaneously hypertensive rats) potentially usefull for the treatment of vascular wall hypertrophy. Other representative compounds from this series of imidazole derivatives include the following:



Compound	R1	R2	X	Formula
268033	Me	t-BuOCO		C ₂₁ H ₂₇ N ₃ O ₆
268034	H	t-BuOCO		C ₂₀ H ₂₅ N ₃ O ₆
268035	Me	CO ₂ Et		C ₁₉ H ₂₃ N ₃ O ₆
268036	H	CO ₂ Et		C ₁₈ H ₂₁ N ₃ O ₆
268037	CO ₂ Et	CO ₂ Et		C ₂₁ H ₂₅ N ₃ O ₈
268038	H	CN		C ₁₆ H ₁₆ N ₄ O ₄
268039	Et	CO ₂ Et		C ₂₀ H ₂₅ N ₃ O ₆
268040	CONH ₂	CO ₂ Et	HCl	C ₁₉ H ₂₂ N ₄ O ₇ .HCl
268041	i-Pr	CO ₂ Et	HCl	C ₂₁ H ₂₇ N ₃ O ₆ .HCl

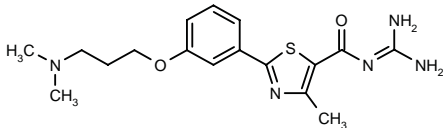
SOURCE – Kissei.

REFERENCES

1. Harada, H. et al. (Kissei Pharmaceutical Co., Ltd.) *Imidazole derivs.* JP 98212278.

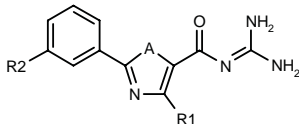
268219

N²-[2-[3-[3-(Dimethylamino)propoxy]phenyl]-4-methylthiazol-5-ylcarbonyl]guanidine

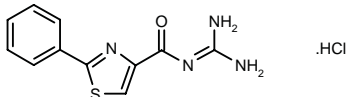


C17 H23 N5 O2 S; Mol wt: 361.4677

ACTION – An inhibitor of Na⁺/H⁺ exchange with potential in the treatment or prevention of angina pectoris, myocardial infarction, arrhythmia, hypertension, atherosclerosis and complications of diabetes. Other compounds from this series of heteroarylcarbonyl-guanidines include the following:



Compound	R1	R2	A	Formula
268220	Me	1-imidazolyl-CH ₂ CH ₂ O	S	C ₁₇ H ₁₈ N ₆ O ₂ S
268221	Me	Me	S	C ₁₃ H ₁₄ N ₄ OS
268222	Me	1-Me-4-Pip-O	S	C ₁₈ H ₂₃ N ₆ O ₂ S
268223	CF ₃	O(CH ₂) ₄ N(Me) ₂	S	C ₁₈ H ₂₂ F ₃ N ₅ O ₂ S
268225	Me	4-morpholinyl-(CH ₂) ₄ O	O	C ₂₀ H ₂₇ N ₅ O ₄



268224: C11 H10 N4 OS . HCl

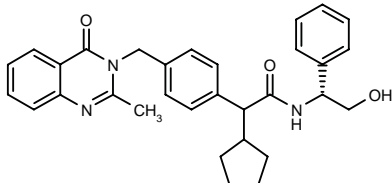
SOURCES – Merck KGaA; Yamanouchi.

REFERENCES

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268674

2-Cyclopentyl-N-[2-hydroxy-1(*R*)-phenylethyl]-2-[4-(2-methyl-4-oxo-3,4-dihydroquinazolin-3-ylmethyl)-phenyl]acetamide



C31 H33 N3 O3; Mol wt: 495.6197

ACTION – Agent for the treatment of atherosclerosis, obesity, pancreatitis and constipation that acts by inhibiting the formation and/or release of apolipoprotein B-100 (ApoB-100)-associated lipoproteins, as shown *in vitro* in cultured hepatic HepG2 cells (IC₅₀ = 44.4 nM), resulting in a reduction in plasma VLDL levels and subsequent reductions in plasma levels of ApoB-100, LDL, triglycerides and cholesterol.

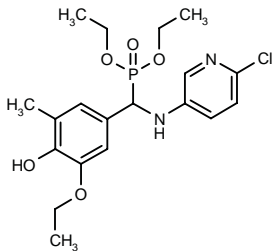
SOURCE – Bayer.

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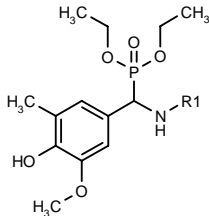
268694

1-(6-Chloropyridin-3-ylamino)-1-(3-ethoxy-4-hydroxy-5-methylphenyl)methylphosphonic acid diethyl ester



C19 H26 Cl N2 O5 P; Mol wt: 428.8504

ACTION – Lipoprotein(a) (Lp[a])-lowering agent, as demonstrated *in vitro* in cynomolgus monkey hepatocytes and *in vivo* in cynomolgus monkeys, where it lowered plasma Lp(a) by 20% on day 28 when given at 25 mg/kg/day p.o. x 4 weeks. Potentially useful for the treatment of atherosclerosis, thrombosis and restenosis following angioplasty. Other compounds from this series of aminophosphonic acid derivatives include the following:



Compound	R1	Formula
268695	6-MeO-3-Pyr	C ₁₉ H ₂₇ N ₂ O ₆ P
268696	6-Cl-3-Pyr	C ₁₈ H ₂₄ ClN ₂ O ₅ P
268697	2-Cl-3-Pyr	C ₁₈ H ₂₄ ClN ₂ O ₅ P

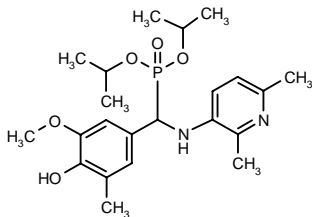
SOURCES – SmithKline Beecham; Symphar.

REFERENCES

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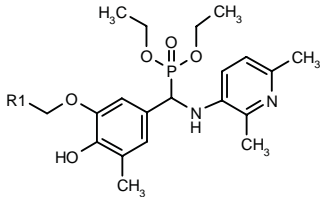
268702

1-(2,6-Dimethylpyridin-3-ylamino)-1-(4-hydroxy-3-methoxy-5-methylphenyl)methylphosphonic acid diisopropyl ester



C22 H33 N2 O5 P; Mol wt: 436.4857

ACTION – Lipoprotein(a) (Lp[a])-lowering agent, as demonstrated *in vitro* in cynomolgus monkey hepatocytes by a decrease in Lp(a) secretion of 20-50% at 20 μM, and *in vivo* in cynomolgus monkeys, where it lowered plasma Lp(a) by 15-27% on day 28 when given at 25 mg/kg/day p.o. x 4 weeks. Potentially useful for the treatment of atherosclerosis, thrombosis and restenosis following angioplasty. Other compounds from this series of aminophosphonic acid derivatives include the following:



Compound	R1	Formula
268703	H	C ₂₀ H ₂₉ N ₂ O ₅ P
268704	Me	C ₂₁ H ₃₁ N ₂ O ₅ P

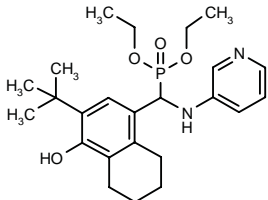
SOURCES – SmithKline Beecham; Symphar.

REFERENCES

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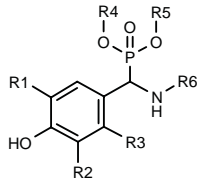
268707

1-(3-*tert*-Butyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)-1-(3-pyridylamino)methylphosphonic acid diethyl ester



C24 H35 N2 O4 P; Mol wt: 446.5245

ACTION – Lipoprotein(a) (Lp[a])-lowering agent, as demonstrated *in vitro* in cynomolgus monkey hepatocytes (19-22% decrease in Lp[a] secretion at 20 μM) and *in vivo* in cynomolgus monkeys, where it lowered plasma Lp(a) by 35-40% on day 28 when given at 25 mg/kg/day p.o. x 4 weeks. Potentially useful for the treatment of atherosclerosis, thrombosis and restenosis following angioplasty. Other compounds from this series of aminophosphonic acid derivatives include the following:



Compound	R1	R2	R3	R4=R5	R6	Formula
268708	t-Bu	-(CH2)4-	Me	Me	3-Pyr	C ₂₂ H ₃₁ N ₂ O ₄ P
268709	t-Bu	-(CH2)4-	i-Pr	i-Pr	3-Pyr	C ₂₆ H ₃₉ N ₂ O ₄ P
268710	t-Bu	-(CH2)4-	Et	Et	2-Pyr	C ₂₄ H ₃₅ N ₂ O ₄ P
268711	Me	Me	Me	Et	3-Pyr	C ₁₉ H ₂₇ N ₂ O ₄ P

SOURCES – SmithKline Beecham; Symphar.

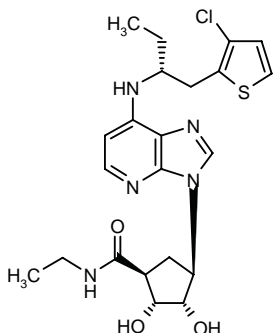
REFERENCES

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AMP-579

267815

[1*S*-[1 α ,2 β ,3 β ,4 α (*R*)]-4-[7-[1-(3-Chloro-2-thienyl-methyl)propylamino]-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-*N*-ethyl-2,3-dihydroxycyclopentane-1-carboxamide



C22 H28 Cl N5 O3 S; Mol wt: 478.0142

ACTION – Cardioprotective agent, an adenosine A₁/A_{2a} receptor agonist (K_i = 5 and 56 nM, respectively) shown to provide marked cardioprotection in a model of myocardial infarction in pigs subjected to coronary artery occlusion followed by reperfusion, reducing infarct size by 98% when given at a dose of 3 μ g/kg i.v. 3 min before ischemia followed by 0.3 μ g/kg/min through 1 h of reperfusion, without altering blood pressure, heart rate or coronary blood flow; it also prevented ventricular fibrillation during ischemia, observed in 90% of control pigs. The compound was also protective (50% reduction in infarct size) when administered 30 min after the onset of myocardial ischemia (10 min before reperfusion) at doses of 3 μ g/kg + 0.3 μ g/kg/min and 30 μ g/kg + 3 μ g/kg/min through 1 h of reperfusion. Its protective effect appeared to be a result of adenosine receptor stimulation and not to changes in afterload or myocardial oxygen demand. Potentially useful for the treatment of acute myocardial infarction.

SOURCE – Rhône-Poulenc Rorer.

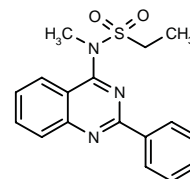
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ANTIARRHYTHMIC DRUGS

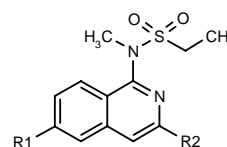
265433

N-Methyl-*N*-(2-phenylquinazolin-4-yl)ethanesulfonamide

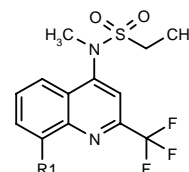


C17 H17 N3 O2 S; Mol wt: 327.4063

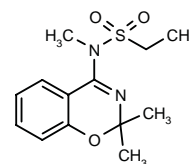
ACTION – Antiarrhythmic agent that acts by virtue of its K_{V(s)} channel-blocking activity. Other exemplified sulfonamide derivatives include the following:



Compound	R1	R2	Formula
266671	H	Cl	C ₁₂ H ₁₃ ClN ₂ O ₂ S
266672	Cl	H	C ₁₂ H ₁₃ ClN ₂ O ₂ S



Compound	R1	Formula
266674	H	C ₁₃ H ₁₃ F ₃ N ₂ O ₂ S
266675	Cl	C ₁₃ H ₁₂ ClF ₃ N ₂ O ₂ S



266673: C13 H18 N2 O3 S

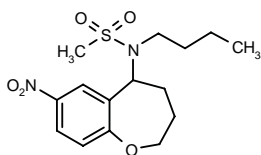
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Brendel, J. et al. (Hoechst AG) *Sulfonamide substd. cpds. as K-channel blockers.* EP 847996, JP 98182610, US 5856338.

268208

N-Butyl-*N*-(7-nitro-2,3,4,5-tetrahydro-1-benzoxepin-5-yl)methanesulfonamide



C₁₅ H₂₂ N₂ O₅ S; Mol wt: 342.4138

ACTION – Agent for the treatment or prevention of cardiovascular disorders, particularly arrhythmias, as well as gastrointestinal disorders such as ulcers and reflux esophagitis, and diarrhea, a potassium channel blocker acting on cAMP-dependent potassium channels. Compound exhibited an IC₅₀ value of 3.3 μM for inhibition of human K_{V(s)} channels expressed in *Xenopus* oocytes.

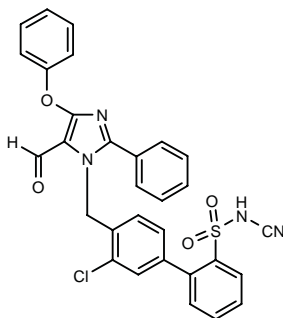
SOURCE – Hoechst Marion Roussel.

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1. Brendel, J. et al. (Hoechst AG) Sulfonamido subst. condensed, seven-membered ring cpds. with potassium channel blocking activity. EP 861836, JP 98287641.

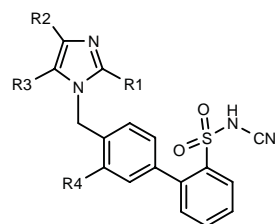
268347

3'-Chloro-*N*-cyano-4'-(5-formyl-4-phenoxy-2-phenyl-1*H*-imidazol-1-ylmethyl)-1,1'-biphenyl-2-sulfonamide



C₃₀ H₂₁ Cl N₄ O₄ S; Mol wt: 569.0389

ACTION – Antiarrhythmic agent with a cardioprotective component and additional activity as an inhibitor of cell proliferation. *In vitro*, compound inhibited Na⁺-dependent Cl⁻/HCO₃⁻ exchange (NCBE) in human endothelial cells (about 97% inhibition at a concentration of 10 μM). Claimed for the treatment or prevention of ischemic disorders, myocardial infarction, angina pectoris, shock states, respiratory disorders and proliferative disorders. Other compounds form this series of *N*-cyanosulfamoyl-biphenylmethylimidazoles include the following:



Compound	R1	R2	R3	R4	Formula
268348	Ph	Cl	CHO	Cl	C ₂₄ H ₁₆ Cl ₂ N ₄ O ₃ S
268349	Ph	Cl	CHO	F	C ₂₄ H ₁₆ ClFN ₄ O ₃ S
268350	Ph	OMe	CHO	Cl	C ₂₅ H ₁₉ ClN ₄ O ₄ S
268351	Pr	SMe	CO ₂ Et	H	C ₂₄ H ₂₆ N ₄ O ₄ S ₂

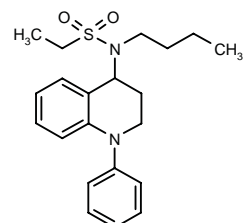
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Kleemann, H.-W. et al. (Hoechst AG) Five-membered heterocycles having biphenylsulphonyl substituents, processes for the preparation thereof, their use as medicaments or diagnostic agent and medicaments containing them. EP 855392.

268668

N-Butyl-*N*-(1-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-ethanesulfonamide



C₂₁ H₂₈ N₂ O₂ S; Mol wt: 372.5302

ACTION – Agent for the treatment or prevention of cardiovascular disorders, particularly arrhythmias, as well as gastrointestinal disorders such as ulcers and reflux esophagitis, and diarrhea, a potassium channel blocker acting on cAMP-dependent potassium channels.

SOURCE – Hoechst Marion Roussel.

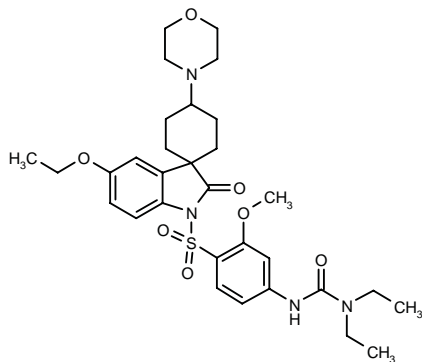
REFERENCES

1. Gerlach, U. et al. (Hoechst AG) Sulfonamide subst. cpds., process for their preparation, their use as medicine or for diagnostic purpose. EP 857724, JP 98218855.

HEART FAILURE THERAPY

268181

N-[4-[5'-Ethoxy-4-(4-morpholinyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-1'-ylsulfonyl]-3-methoxyphenyl]-*N*',*N*'-diethylurea



C31 H42 N4 O7 S; Mol wt: 614.7598

ACTION – Agent with affinity for vasopressin V_2 and/or oxytocin receptors, potentially useful in the treatment of vasopressin- or oxytocin-dependent disorders including cardiovascular disorders such as heart failure and hypertension, migraine, cerebral edema, depression, anxiety, renal disorders, gastrointestinal disorders and sexual dysfunction. A representative compound from a series of indolin-2-one derivatives.

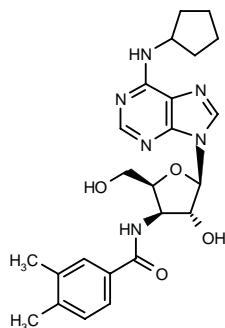
SOURCE – Sanofi.

REFERENCES

1. Foulon, L. et al. (Sanofi) *Indolin-2-one derivs., method for preparing them and pharmaceutical compns. containing them.* WO 9825901.

268337

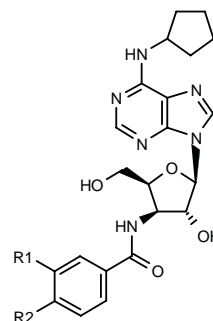
*N*⁶-Cyclopentyl-9-[3-deoxy-3-(3,4-dimethylbenzamido)-β-D-xylofuranosyl]adenine



C24 H30 N6 O4; Mol wt: 466.5390

ACTION – Adenosine analog with potent affinity for adenosine A_1 receptors and 160-fold selectivity over A_{2a} receptors; compound was found to behave as a full antagonist at A_1 receptors, as demonstrated by K_i values for A_1 receptors in the absence or presence of GTP of 0.0236 ± 0.0025 and 0.0174 ± 0.0042 μ M, respectively. Potentially useful as a cardiotonic, renal protectant,

cognition-enhancing and/or antiasthmatic agent. Other specifically claimed compounds from this series of adenosine analogs include the following:



Compound	R1	R2	Formula
268338	H	Me	$C_{23}H_{28}N_6O_4$
268339	Cl	Cl	$C_{22}H_{24}Cl_2N_6O_4$

SOURCES – Katholieke Universiteit Leuven, Leuven (NL); Leiden University, Leiden (NL).

REFERENCES

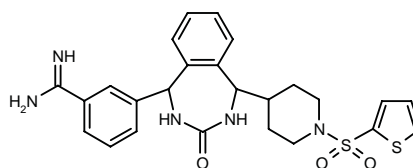
1. Herdewijn, P.A.M.M. and Ijzerman, A.P. (Katholieke Universiteit Leuven; Leiden University) *Cpds. derived from adenosine, use of such cpd. as a medicament, method for synthesizing such a compound and intermediates thereof.* EP 863148.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

267682

3-[3-Oxo-5-[1-(2-thienylsulfonyl)piperidin-4-yl]-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-yl]benzene-carboximidamide



C25 H27 N5 O3 S2; Mol wt: 509.6523

ACTION – Orally available anticoagulant, a potent and selective factor Xa inhibitor ($K_i = 2.5$ nM vs. 300 and 31 nM, respectively, for thrombin and trypsin) from a series of cycloheptylureas with high activity in the AV shunt model of thrombosis in rabbits ($ID_{50} = 1.2$ μ mol/kg/h i.v.).

SOURCE – DuPont Pharmaceuticals.

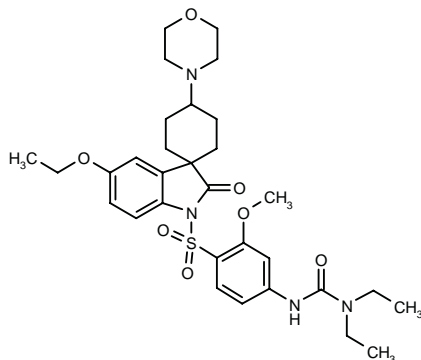
REFERENCES

1. Galemme, R.A. Jr. et al. *The design and synthesis of cycloheptylurea inhibitors of factor Xa.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abstr P.46.

HEART FAILURE THERAPY

268181

N-[4-[5'-Ethoxy-4-(4-morpholinyl)-2'-oxospiro[cyclohexane-1,3'-indolin]-1'-ylsulfonyl]-3-methoxyphenyl]-*N*',*N*'-diethylurea



C31 H42 N4 O7 S; Mol wt: 614.7598

ACTION – Agent with affinity for vasopressin V_2 and/or oxytocin receptors, potentially useful in the treatment of vasopressin- or oxytocin-dependent disorders including cardiovascular disorders such as heart failure and hypertension, migraine, cerebral edema, depression, anxiety, renal disorders, gastrointestinal disorders and sexual dysfunction. A representative compound from a series of indolin-2-one derivatives.

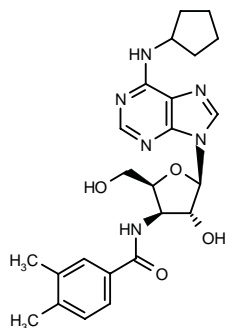
SOURCE – Sanofi.

REFERENCES

1. Foulon, L. et al. (Sanofi) *Indolin-2-one derivs., method for preparing them and pharmaceutical compns. containing them.* WO 9825901.

268337

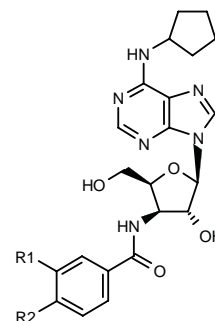
*N*⁶-Cyclopentyl-9-[3-deoxy-3-(3,4-dimethylbenzamido)-β-D-xylofuranosyl]adenine



C24 H30 N6 O4; Mol wt: 466.5390

ACTION – Adenosine analog with potent affinity for adenosine A_1 receptors and 160-fold selectivity over A_{2a} receptors; compound was found to behave as a full antagonist at A_1 receptors, as demonstrated by K_i values for A_1 receptors in the absence or presence of GTP of 0.0236 ± 0.0025 and 0.0174 ± 0.0042 μ M, respectively. Potentially useful as a cardiotonic, renal protectant,

cognition-enhancing and/or antiasthmatic agent. Other specifically claimed compounds from this series of adenosine analogs include the following:



Compound	R1	R2	Formula
268338	H	Me	$C_{23}H_{28}N_6O_4$
268339	Cl	Cl	$C_{22}H_{24}Cl_2N_6O_4$

SOURCES – Katholieke Universiteit Leuven, Leuven (NL); Leiden University, Leiden (NL).

REFERENCES

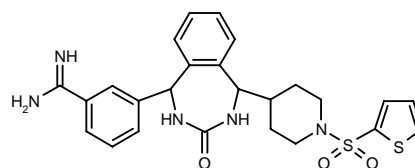
1. Herdewijn, P.A.M.M. and Ijzerman, A.P. (Katholieke Universiteit Leuven; Leiden University) *Cpds. derived from adenosine, use of such cpd. as a medicament, method for synthesizing such a compound and intermediates thereof.* EP 863148.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

267682

3-[3-Oxo-5-[1-(2-thienylsulfonyl)piperidin-4-yl]-2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-yl]benzene-carboximidamide



C25 H27 N5 O3 S2; Mol wt: 509.6523

ACTION – Orally available anticoagulant, a potent and selective factor Xa inhibitor ($K_i = 2.5$ nM vs. 300 and 31 nM, respectively, for thrombin and trypsin) from a series of cycloheptylureas with high activity in the AV shunt model of thrombosis in rabbits ($ID_{50} = 1.2$ μ mol/kg/h i.v.).

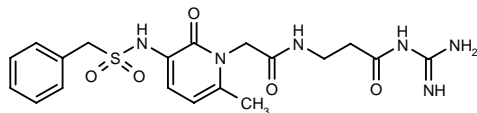
SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Galembo, R.A. Jr. et al. *The design and synthesis of cycloheptylurea inhibitors of factor Xa.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abstr P.46.

267689

3-(Benzylsulfonylamino)-*N*-(3-guanidino-3-oxopropyl)-6-methyl-2-oxo-1,2-dihydropyridine-1-acetamide



C19 H24 N6 O5 S; Mol wt: 448.5016

ACTION – Potent, nonpeptide, acylguanidine-containing thrombin inhibitor with no activity against factor Xa.

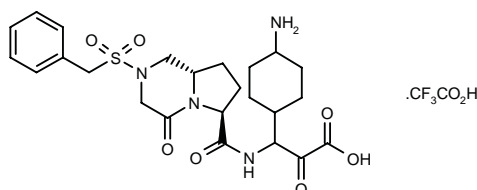
SOURCE – Organon.

REFERENCES

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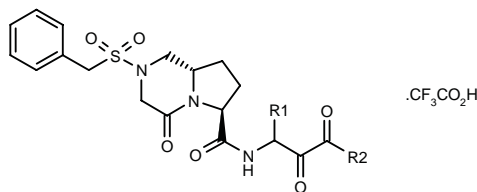
268712

(6*S*,8*aS*)-3-(4-Aminocyclohexyl)-3-[2-(benzylsulfonyl)perhydropyrrolo[1,2-*a*]pyrazin-6-ylcarboxamido]-2-oxopropionic acid trifluoroacetate



C24 H32 N4 O7 S . C2 H F3 O2; Mol wt: 634.6257

ACTION – Anticoagulant and antithrombotic agent, a potent and selective thrombin inhibitor ($K_i = 0.09$ nM; K_i trypsin/ K_i thrombin = 24,000). A representative compound from a series of bicyclic inhibitors, wherein the following are also included:



Compound	R1	R2	Formula
268713	4-NH2-cyclohexyl	OMe	C ₂₅ H ₃₄ N ₄ O ₇ S.C ₂ HF ₃ O ₂
268714	trans-4-NH2-cyclohexyl	NHMe	C ₂₅ H ₃₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂
268715	4-NH2-cyclohexyl	NHCH2-CO2H	C ₂₆ H ₃₅ N ₅ O ₆ S.C ₂ HF ₃ O ₂

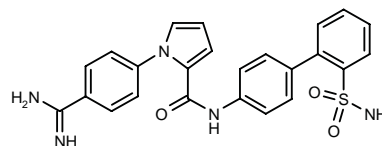
SOURCE – BioChem Pharma.

REFERENCES

1. Bachand, B. et al. (BioChem Pharma Inc.) *Bicyclic thrombin inhibitors*. WO 9828326.

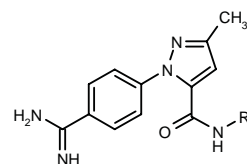
268974

1-(4-Amidinophenyl)-*N*-(2'-sulfamoylbiphenyl-4-yl)pyrrole-2-carboxamide



C24 H21 N5 O3 S; Mol wt: 459.5279

ACTION – Anticoagulant and antithrombotic agent, an inhibitor of trypsin-like serine proteases, particularly factor Xa. Other specifically claimed compounds within this series of nitrogenated heteroaryl derivatives include the following:



Compound	R1	Formula
268975	4-(2-CF3-Ph)-2-Cl-Ph	C ₂₅ H ₁₉ ClF ₃ N ₅ O
268976	5-(2-MeSO2-Ph)-2-Pyr	C ₂₄ H ₂₂ N ₅ O ₃ S
268977	4-(1-pyrrolidinyl-CH2)-Ph	C ₂₃ H ₂₈ N ₆ O

SOURCE – DuPont Pharmaceuticals.

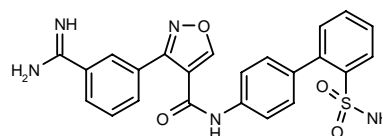
REFERENCES

1. Pinto, D.J.P. et al. (The Du Pont Merck Pharmaceutical Co.) *Nitrogen containing heteroaromatics as factor Xa inhibitors*. WO 9828269.

SA-862

267438

3-(3-Amidinophenyl)-*N*-(2'-sulfamoylbiphenyl-4-yl)-isoxazole-4-carboxamide



C23 H19 N5 O4 S; Mol wt: 461.5001

ACTION – Potent factor Xa inhibitor from a series of isoxazolines and isoxazoles, with K_i values for factor Xa, thrombin and trypsin of 0.15, 2000 and 21 nM, respectively. SA-862 was highly effective in the AV shunt model of thrombosis in rabbits ($ID_{50} = 0.31$ μ mol/kg/h) and it showed favorable pharmacokinetics in dogs, with a half-life of 4.3 h and a volume of distribution of 1.7 l/g.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

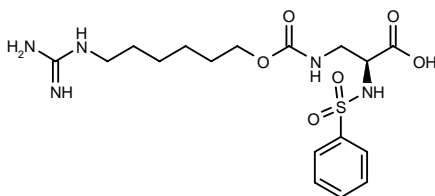
1. Pruitt, J.R. et al. (The Du Pont Merck Pharmaceutical Co.) *Oxygen or sulfur containing heteroaromatics as factor Xa inhibitors*. WO 9828282.

2. Pruitt, J.R. et al. *Isoxazolines and isoxazoles as factor Xa inhibitors*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 077.

ANTIPLATELET THERAPY

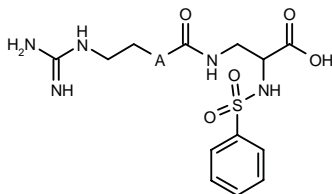
267775

3-(6-Guanidinohexyloxycarbonylamino)-2(*S*)-(phenylsulfonamido)propionic acid

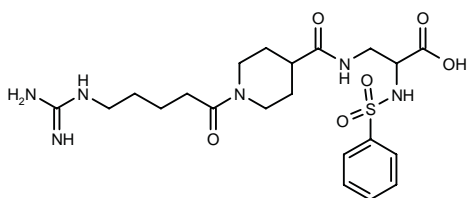


C17 H27 N5 O6 S; Mol wt: 429.4953

ACTION – Agent for the treatment of thrombosis and restenosis that inhibits the adhesive function of various RGD-dependent integrins. In particular, the compound is a nonspecific inhibitor of the platelet fibrinogen (gplIb/IIIa) and the vitronectin $\alpha_v\beta_3$ receptor ($IC_{50} = 0.01$ and 0.01 μ M, respectively). It also inhibits ADP-induced human platelet aggregation ($IC_{50} = 0.04$ μ M). Within this series of specifically claimed α -sulfonamido- and α -sulfinamido-containing carboxylic acid compounds, the following are also included:



Compound	A	Isomer	Formula
267776	-(CH2)5-		C ₁₈ H ₂₉ N ₅ O ₅ S
267778	-(CH2)4NH-	S	C ₁₇ H ₂₈ N ₆ O ₅ S
267779	-CH2CH2OCH2CH2O-	S	C ₁₇ H ₂₇ N ₅ O ₇ S
267780	-O(CH2)4O-	S	C ₁₇ H ₂₇ N ₅ O ₇ S
267781	-(CH2)3OCH2-	S	C ₁₇ H ₂₇ N ₅ O ₆ S
267782	-(CH2)4OCH2-	S	C ₁₈ H ₂₉ N ₅ O ₆ S



267777: C21 H32 N6 O6 S

SOURCES – COR Therapeutics; Lilly.

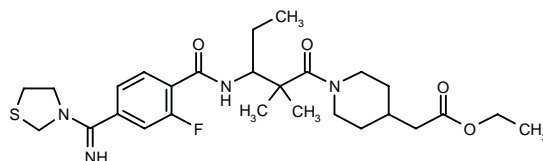
REFERENCES

1. Fisher, M.J. et al. (Eli Lilly and Company;COR Therapeutics, Inc.) *Integrin antagonists*. WO 9825892.

NSL-96184

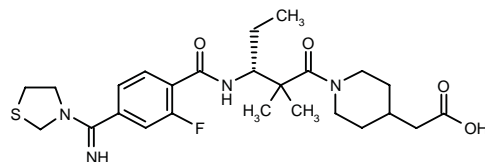
265678

1-[3-[2-Fluoro-4-(thiazolidin-3-ylcarboimidoyl)benzamido]-2,2-dimethylpentanoyl]piperidine-4-acetic acid ethyl ester



C27 H39 F N4 O4 S; Mol wt: 534.6931

ACTION – Highly potent, orally active fibrinogen (gplIb/IIIa) receptor antagonist characterized by the presence of a trisubstituted β -amino acid residue, with potential as an antithrombotic agent in the acute phase. It gave an IC_{50} value in the ELISA gplIb/IIIa binding assay of 2.3 ± 0.50 nM and of 0.045 ± 0.004 μ M for inhibition of collagen-induced human platelet aggregation. In guinea pigs, it displayed a fast onset of action ($t_{max} = 30$ min) and a relatively short duration of action ($t_{1/2\beta} = 110$ min) following oral administration. Its biologically active form was found to be the (*R*)-free acid:



264743: C25 H35 F N4 O 4S

SOURCE – Nippon Steel.

REFERENCES

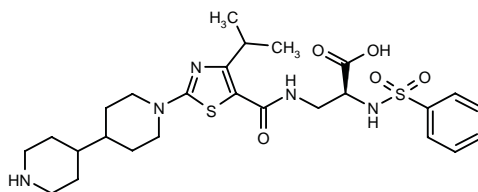
1. Hayashi, Y. et al. (Nippon Steel Corp.) *Fibrinogen receptor antagonists and medicinal preparations containing the same as the active ingredient*. EP 852225, JP 98017550, WO 9749682.

2. Hayashi, Y. et al. *GP1Ib/IIIa integrin antagonists with the new conformational restriction unit, trisubstituted beta-amino acid derivatives, and substituted benzamidine structure*. J Med Chem 1998, 41(12): 2345.

UR-12947

267439

3-[4-Isopropyl-2-[4-(4-piperidinyl)piperidin-1-yl]thiazol-5-ylcarboxamido]-2(*S*)-(phenylsulfonamido)propionic acid



C26 H37 N5 O5 S2; Mol wt: 563.7403

ACTION – Orally active fibrinogen (gpIIb/IIIa) receptor antagonist with an IC_{50} of 3.5 nM for inhibition of ADP-induced human platelet aggregation, proven to inhibit *ex vivo* platelet aggregation in dogs and monkeys by 90-100% at 2 h at respective doses of 0.1 and 0.3 mg/kg p.o.; 40 and 25% inhibition, respectively, was still observed at 24 h after these doses. Selected as a development candidate from a series of *N*-(thiazolyl-5-carbonyl)- β -alanine derivatives.

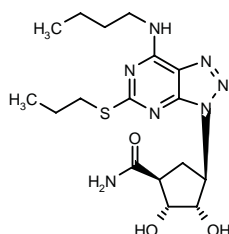
SOURCE – Uriach.

REFERENCES

1. Carceller, E. et al. (J. Uriach & Cia. SA) *Novel carboxamides as platelet aggregation inhibitors*. WO 9846599.
2. Carceller, E. et al. *Novel N-(thiazolyl-5-carbonyl)- β -alanine derivatives as potent, orally active fibrinogen receptor antagonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 079.

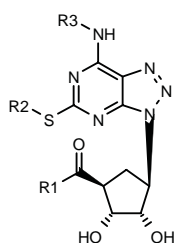
268936

[1*S*-(1 α ,2 β ,3 β ,4 α)]-4-[7-(Butylamino)-5-(propylsulfanyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxy-cyclopentanecarboxamide



C18 H28 N6 O3 S; Mol wt: 408.5242

ACTION – Platelet aggregation inhibitor and antithrombotic agent that acts as an antagonist of the P2T purinoceptor and is expected to show improved efficacy compared to aspirin. A representative compound from a series of triazolo[4,5-*d*]pyrimidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
268937	NH2	Pr	CH2CH2-SMe	C ₁₆ H ₂₆ N ₇ O ₃ S ₂
268938	NHCH2CH2OH	Pr	Bu	C ₁₉ H ₃₁ N ₇ O ₄ S
268939	-D-Ser-NH2	4-CF3-Ph	Bu	C ₂₄ H ₂₉ F ₃ N ₈ O ₅ S
268940	OH	CH2CH2-CF3	Bu	C ₁₇ H ₂₃ F ₃ N ₆ O ₄ S
268941	OH	Pr	cyclopentyl	C ₁₈ H ₂₆ N ₆ O ₄ S
268942	NHCH2-CON(Me)2	Pr	Bu	C ₂₁ H ₃₄ N ₈ O ₄ S
268943	OH	Pr	1-Ph-cyclo-propyl	C ₂₂ H ₂₆ N ₆ O ₄ S
268944	3,4-(OH)2-PhCH2NH	Pr	Bu	C ₂₄ H ₃₃ N ₇ O ₅ S
268945	OH	Pr	CH2CH2-NHPh	C ₂₁ H ₂₇ N ₇ O ₄ S

SOURCE – Astra.

REFERENCES

1. Bonnert, R. et al. (Astra AB; Astra Pharmaceuticals Ltd.) *Triazolo[4,5-*d*]pyrimidinyl derivs. and their use as medicaments*. WO 9828300.

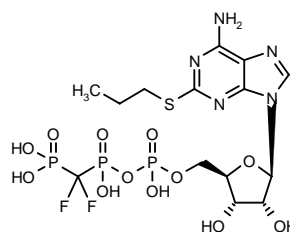
AR-C66096

267910

5'-O-[[[Difluoro(phosphono)methyl](hydroxy)phosphoryloxy]-(hydroxy)phosphoryl]-2-(propylsulfanyl)adenosine

ARL-66096

FPL-66096 (formerly)



C14 H22 F2 N5 O12 P3 S; Mol wt: 615.3348

ACTION – Highly potent, selective and competitive human platelet P2T purinoceptor antagonist, an ATP analog that acts as a potent and selective inhibitor of ADP-induced platelet aggregation ($pK_B = 8.66$ in washed human platelets); it shows weak agonist activity at P2X receptors ($pA_{50} = 3.68$ in rabbit ear artery) and weak antagonist activity at P2Y receptors (apparent $pK_B = 4.71$ in guinea pig aorta), indicating a selectivity of at least 9000-fold for the P2T subtype. Platelets pretreated with AR-C66096 at concentrations of 100-200 nmol/l showed marked loss of platelet aggregation and activation responses to serum from patients with heparin-induced thrombocytopenia (HIT). It thus appears that this compound may be useful both as a pharmacological tool for elucidating the mechanisms of ADP-induced platelet activation and as a potential therapy for preventing or treating complications associated with heparin therapy.

SOURCE – Astra Charnwood.

REFERENCES

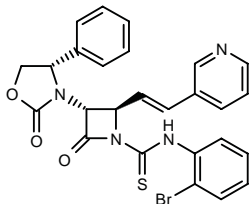
1. Ingall, A.H. and Cage, P.A. (Fisons plc) *ATP analogues*. EP 508687, US 5654285.
2. Fagura, M.S. et al. *P2Y1-receptors in human platelets which are pharmacologically distinct from P2Y ADP-receptors*. Br J Pharmacol 1998, 124(1): 157.
3. Humphries, R.G. et al. *A novel series of P2T purinoceptor antagonists: Definition of the role of ADP in arterial thrombosis*. Trends Pharmacol Sci 1995, 179.
4. Humphries, R.G. et al. *FPL 66096: A novel, highly potent and selective antagonist at human platelet P2T-purinoceptors*. Br J Pharmacol 1994, 113(3): 1057.
5. Polgár, J. et al. *Adenosine diphosphate (ADP) and ADP receptor play a major role in platelet activation/aggregation induced by sera from heparin-induced thrombocytopenia patients*. Blood 1998, 91(2): 549.
6. Tomlinson, W. et al. *ARL 67085 and ARL 66096 are slowly dissociating competitive P2T-purinoceptor antagonists*. Br J Pharmacol 1997, 120(Suppl.): Abst 131P.
7. Webb, R.J. and Watson, S.P. *The P2T-receptor and P2Y1 receptor are both involved in ADP-induced Ca2+-elevation in human washed platelets*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 10.3.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

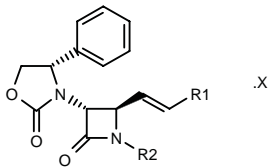
267757

trans-*N*-(2-Bromophenyl)-2-oxo-3(*R*)-[4(*S*)-phenyl-oxazolidin-3-yl]-4(*R*)-[2-(3-pyridyl)vinyl]azetidine-1-carbothioamide

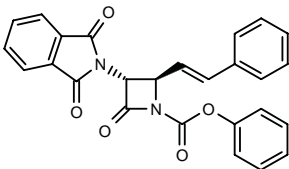


C26 H21 Br N4 O3 S; Mol wt: 549.4469

ACTION – Agent for the treatment of prostatic cancer and metastasis, benign prostatic hyperplasia and breast cancer, an inhibitor of the proteolytic activity of prostate-specific antigen (PSA; IC₅₀ = 0.0353 μM in a colorimetric assay). Within this series of azetidinone derivatives, the following are also included:



Compound	R1	R2	X	Formula
267759	3-Pyr	CO2Ph	HCl	C ₂₆ H ₂₁ N ₃ O ₅ .HCl
267760	3-quinolinyl	CO2Ph	HCl	C ₃₀ H ₂₃ N ₃ O ₅ .HCl
267761	3-Pyr	CO2Ph	acetate	C ₂₆ H ₂₁ N ₃ O ₅ .C ₂ H ₄ O ₂
267762	3-MeO-Ph	CO2Ph		C ₂₈ H ₂₄ N ₂ O ₆
267763	3-Pyr	4,6-(MeO)2-1,3,5-triazin-2-yl		C ₂₄ H ₂₂ N ₆ O ₅
267764	3-Pyr	CSNHPh		C ₂₆ H ₂₂ N ₄ O ₃ S



267758: C26 H18 N2 O5

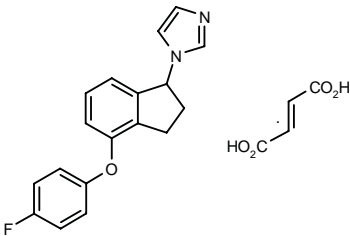
SOURCE – Lilly.

REFERENCES

1. Anderson, B.A. et al. (Eli Lilly and Company) *Inhibitors of the enzymatic activity of PSA*. WO 9825895.

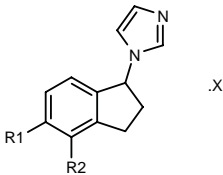
267879

1-[4-(4-Fluorophenoxy)indan-1-yl]imidazole fumarate



C18 H15 F N2 O . C4 H4 O4; Mol wt: 410.3991

ACTION – Agent for the treatment of benign prostatic hypertrophy, prostate cancer and breast cancer, a potent steroid C_{17,20} lyase inhibitor (IC₅₀ = 22 nM in rat testis). Other compounds from this series of fused benzene derivatives include the following:



Compound	R1	R2	X	Formula
267880	Ph	H	fumarate	C ₁₈ H ₁₆ N ₂ .C ₄ H ₄ O ₄
267881	4-F-Ph	H	fumarate	C ₁₈ H ₁₅ FN ₂ .C ₄ H ₄ O ₄
267882	4-Me-Ph	H	fumarate	C ₁₉ H ₁₈ N ₂ .C ₄ H ₄ O ₄
267883	H	OPh		C ₁₈ H ₁₆ N ₂ O
267884	H	3-Me-PhO	fumarate	C ₁₉ H ₁₈ N ₂ O.C ₄ H ₄ O ₄
267885	H	2-Cl-PhCH2O		C ₁₉ H ₁₇ ClN ₂ O

SOURCE – Takeda.

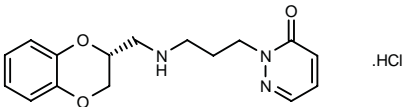
REFERENCES

1. Aono, T. et al. (Takeda Chemical Industries, Ltd.) *Condensed benzene derivs., their preparation method and their agents*. JP 98195056.

GYKI-16084

241391

(*R*)-2-[3-(Benzo-1,4-dioxan-2-ylmethylamino)propyl]-pyridazin-3(2*H*)-one hydrochloride



C16 H19 N3 O3 . HCl; Mol wt: 337.8050

ACTION – Agent for the treatment of benign prostatic hypertrophy (BPH) with selective antagonist activity against postsynaptic α_1 - and α_2 -adrenoceptors and high uroselectivity. It gave pA_2 values, expressing α_1 -adrenoceptor-antagonist potency, of 7.20 and 6.56, respectively, in human prostatic strips and rat mesenteric artery, and selectivity for postjunctional versus prejunctional α_2 -adrenoceptors was demonstrated by pA_2 values of 5.8 and 7.87, respectively, in rat vas deferens and dog saphenous vein. Compound was more selective than tamsulosin and prazosin for improving micturition in normal rats and, in contrast to alfuzosin, it reversed clonidine-induced impairment of voiding in a model of acute BPH in rats. In a model of testosterone-induced BPH in rats, it showed greater uroselectivity compared to alfuzosin and prazosin.

SOURCES – Gedeon Richter; Institute for Drug Research, Budapest (HU).

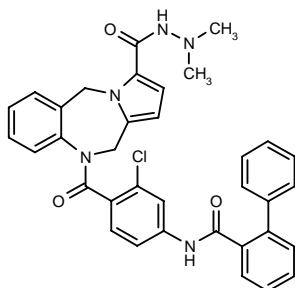
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2. Mátyus, P. et al. GYKI 16084: A new drug candidate for treatment of benign prostatic hyperplasia. 15th EPMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.4.
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4. Institute for Drugs Research, Ltd. Company Profile 1996 September.

DIURETICS

265473

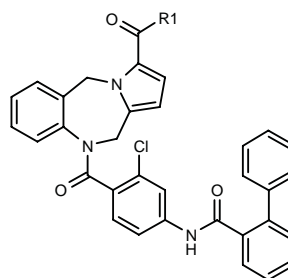
10-[4-(Biphenyl-2-ylcarboxamido)-2-chlorobenzoyl]- N^2, N^2 -dimethyl-10,11-dihydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine-3-carbonohydrazide



C35 H30 Cl N5 O3; Mol wt: 604.1070

ACTION – Potent, nonpeptide vasopressin V_2 receptor antagonist, as demonstrated in a binding assay using murine fibroblast LV-2 cells transfected with the human V_2 receptor ($IC_{50} = 8.6$ nM). *In vivo*, it was shown to potently antagonize the antidiuretic effect of endogenous arginine vasopressin, significantly increasing urine volume in conscious rats at 10 mg/kg p.o. Potentially useful for the treatment of diseases characterized by excess renal water reabsorption such as congestive heart failure, nephrotic syndrome, hyponatremia, coronary vasospasm, cardiac ischemia, renal vasospasm, liver cirrhosis, brain edema,

cerebral ischemia or stroke. Within this series of specifically claimed 5H-pyrrolo[2,1-c][1,4]benzodiazepines, the following are also included:



Compound	R1	Formula
267594	OH	C ₃₃ H ₂₄ ClN ₃ O ₄
267595	4-Me-1-Piz	C ₃₈ H ₃₄ ClN ₃ O ₃
267596	N(Me)CH ₂ CH ₂ N(Me) ₂	C ₃₈ H ₃₆ ClN ₃ O ₃

SOURCE – American Home Products.

REFERENCES

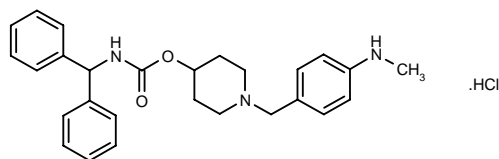
1. Trybulski, E.J. et al. (American Home Products Corp.) 3-Carboxamide derivs. of 5H-pyrrolo[2,1-c][1,4]benzodiazepines. WO 9820011.

TREATMENT OF URINARY INCONTINENCE

YM-58790

267397

N-Benzhydrylcarbamic acid 1-[4-(methylamino)benzyl]-4-piperidiny ester hydrochloride



C27 H31 N3 O2 . HCl; Mol wt: 466.0218

ACTION – Agent for the treatment of urinary incontinence with high affinity for muscarinic M_1 and M_3 receptors ($K_i = 28$ and 15 nM, respectively) and good selectivity relative to M_2 receptors ($K_i = 260$ nM). Although it showed no effect against oxotremorine-induced bradycardia in pithed rats or against the McN-A-343-induced pressor response in pithed rats, it potently inhibited rhythmic bladder contractions in rats ($ED_{30} = 0.36$ mg/kg i.v.); it was less effective against oxotremorine-induced salivation in rats ($ID_{50} = 2.4$ mg/kg i.v.) and it did not inhibit oxotremorine-induced tremor in mice. Compound thus acts as a peripherally active and selective M_3 antagonist *in vivo*, with much greater bladder and receptor subtype selectivity than oxybutynin *in vivo*.

SOURCE – Yamanouchi.

REFERENCES

1. Takeuchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Carbamate deriv. and medicine containing the same*. WO 9506635.

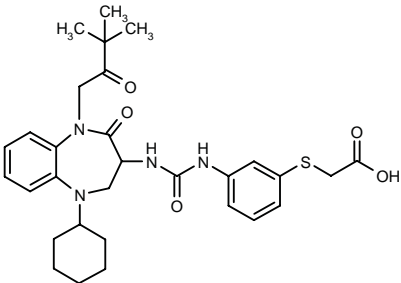
2. Naito, R. et al. *Selective muscarinic antagonists. I. Synthesis and antimuscarinic properties of 4-piperidyl benzhydrylcarbamate derivatives*. Chem Pharm Bull 1998, 46(8): 1274.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

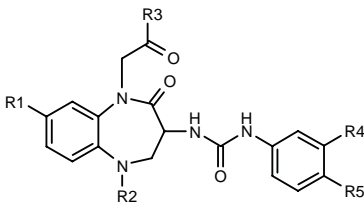
268172

2-[3-[3-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]ureido]-phenylsulfanyl]acetic acid



C30 H38 N4 O5 S; Mol wt: 566.7192

ACTION – Agent for the treatment of gastric ulcers and gastrointestinal motility disorders, a potent and selective CCK_B receptor antagonist ($K_i = 0.1$ nM against [³H]-CCK-8 binding in guinea pig cortex homogenates). *In vivo*, it was found to potently inhibit pentagastrin-induced gastric acid secretion in rats (75.2% inhibition at 1 mg/kg i.d.). Within this series of 1,5-benzodiazepines, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
268173	Me	2-thienyl-CO	2-Me-Ph	CO2H	H	C ₃₂ H ₂₈ N ₄ O ₆ S
268174	Me	t-BuCH2CO	2-Me-Ph	CO2H	Me	C ₃₄ H ₃₈ N ₄ O ₆
268175	H	cyclohexyl	t-Bu	OC(Me)2-CO2H	H	C ₃₂ H ₄₂ N ₄ O ₆
268176	H	cyclohexyl	t-Bu	CO2H	H	C ₂₉ H ₃₆ N ₄ O ₅
268177	H	cyclohexyl	t-Bu	CONH-SO2Me	H	C ₃₀ H ₃₆ N ₅ O ₆ S

SOURCE – Zeria.

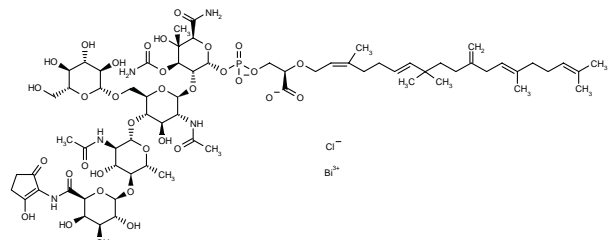
REFERENCES

1. Shinozaki, K. et al. (Zeria Pharmaceutical Co., Ltd.) *1,5-Benzodiazepine derivs*. WO 9825911.

268575

N-(2-Hydroxy-5-oxo-1-cyclopentenyl)-β-D-galactopyranosyluronamide]-(1→4)-*O*-(2-acetamido-2,6-dideoxy-β-D-glucopyranosyl)-(1→4)-*O*-[2-acetamido-2-deoxy-6-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl]-(1→2)-*O*-[1-*O*-[[2(*R*)-carboxy-2-[3,8,8,14,18-pentamethyl-11-methylenonadeca-2(*Z*),6(*E*),13(*E*),17-tetraenyloxy]ethoxy](hydroxy)phosphoryl]-4-*C*-methyl-α-D-glucopyranuronamide chloride bismuth salt

Moenomycin A chloride bismuth salt



C69 H106 Bi Cl N5 O34 P ; Mol wt: 1825.0040

ACTION – Antiulcer agent, a bismuth salt of moenomycin A with more potent anti-*Helicobacter pylori* activity *in vitro* than parent compound (MIC = 0.5 µg/ml against *H. pylori* P 42 vs. 2 µg/ml for moenomycin A sodium salt).

SOURCE – Hoechst Marion Roussel.

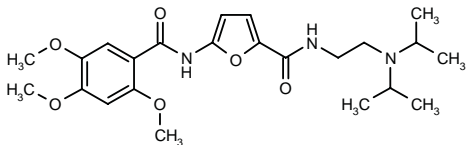
REFERENCES

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TREATMENT OF DISORDERS OF GASTRIC EMPTYING

268028

N-[2-(Diisopropylamino)ethyl]-5-(2,4,5-trimethoxybenzamido)furan-2-carboxamide



C23 H33 N3 O6; Mol wt: 447.5287

ACTION – Gastric prokinetic agent shown to increase contractions in the digestive tract of dogs by 269.3% at a dose of 0.5 mg/kg i.v. No deaths were observed in mice at 500 mg/kg p.o. Other representative compounds within this series of *N*-substituted benzoylamine derivatives include the following:

SOURCE – Yamanouchi.

REFERENCES

1. Takeuchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Carbamate deriv. and medicine containing the same*. WO 9506635.

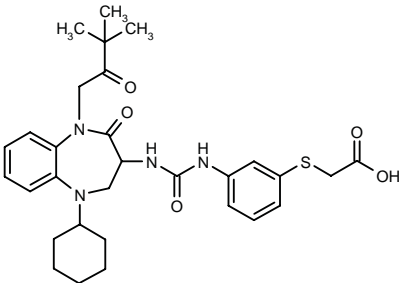
2. Naito, R. et al. *Selective muscarinic antagonists. I. Synthesis and antimuscarinic properties of 4-piperidyl benzhydrylcarbamate derivatives*. Chem Pharm Bull 1998, 46(8): 1274.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

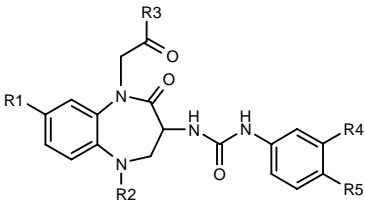
268172

2-[3-[3-[5-Cyclohexyl-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]ureido]-phenylsulfanyl]acetic acid



C30 H38 N4 O5 S; Mol wt: 566.7192

ACTION – Agent for the treatment of gastric ulcers and gastrointestinal motility disorders, a potent and selective CCK_B receptor antagonist ($K_i = 0.1$ nM against [³H]-CCK-8 binding in guinea pig cortex homogenates). *In vivo*, it was found to potently inhibit pentagastrin-induced gastric acid secretion in rats (75.2% inhibition at 1 mg/kg i.d.). Within this series of 1,5-benzodiazepines, the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
268173	Me	2-thienyl-CO	2-Me-Ph	CO2H	H	C ₃₂ H ₂₈ N ₄ O ₆ S
268174	Me	t-BuCH2CO	2-Me-Ph	CO2H	Me	C ₃₄ H ₃₈ N ₄ O ₆
268175	H	cyclohexyl	t-Bu	OC(Me)2-CO2H	H	C ₃₂ H ₄₂ N ₄ O ₆
268176	H	cyclohexyl	t-Bu	CO2H	H	C ₂₉ H ₃₆ N ₄ O ₅
268177	H	cyclohexyl	t-Bu	CONH-SO2Me	H	C ₃₀ H ₃₆ N ₅ O ₆ S

SOURCE – Zeria.

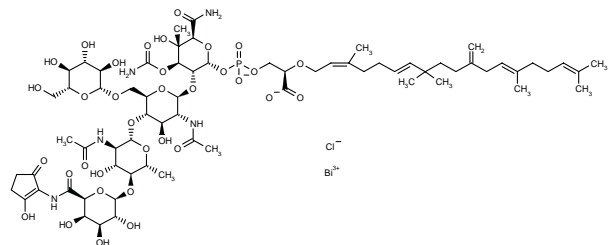
REFERENCES

1. Shinozaki, K. et al. (Zeria Pharmaceutical Co., Ltd.) *1,5-Benzodiazepine derivs*. WO 9825911.

268575

N-(2-Hydroxy-5-oxo-1-cyclopentenyl)-β-D-galactopyranosyluronamide]-(1→4)-*O*-(2-acetamido-2,6-dideoxy-β-D-glucopyranosyl)-(1→4)-*O*-[2-acetamido-2-deoxy-6-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl]-(1→2)-*O*-[1-*O*-[[2(*R*)-carboxy-2-[3,8,8,14,18-pentamethyl-11-methylenonadeca-2(*Z*),6(*E*),13(*E*),17-tetraenyloxy]ethoxy](hydroxy)phosphoryl]-4-*C*-methyl-α-D-glucopyranuronamide chloride bismuth salt

Moenomycin A chloride bismuth salt



C69 H106 Bi Cl N5 O34 P ; Mol wt: 1825.0040

ACTION – Antiulcer agent, a bismuth salt of moenomycin A with more potent anti-*Helicobacter pylori* activity *in vitro* than parent compound (MIC = 0.5 μg/ml against *H. pylori* P 42 vs. 2 μg/ml for moenomycin A sodium salt).

SOURCE – Hoechst Marion Roussel.

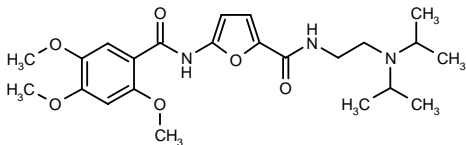
REFERENCES

1. Vértessy, L. et al. (Hoechst AG) *Bismuth salts of moenomycin-like antibiotics, preparation, use and pharmaceuticals containing such salts*. EP 864579.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

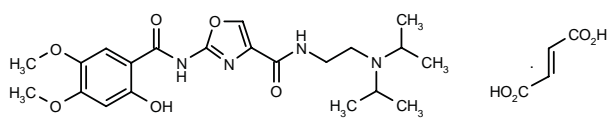
268028

N-[2-(Diisopropylamino)ethyl]-5-(2,4,5-trimethoxybenzamido)furan-2-carboxamide

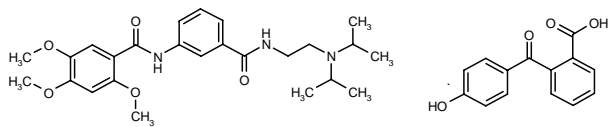


C23 H33 N3 O6; Mol wt: 447.5287

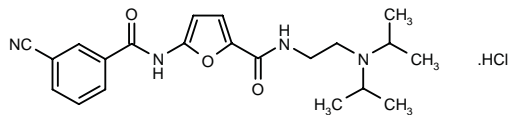
ACTION – Gastric prokinetic agent shown to increase contractions in the digestive tract of dogs by 269.3% at a dose of 0.5 mg/kg i.v. No deaths were observed in mice at 500 mg/kg p.o. Other representative compounds within this series of *N*-substituted benzoylamine derivatives include the following:



268029: C21 H30 N4 O6 . C4 H4 O4



268030: C25 H35 N3 O5 . C4 H10 O4



268031: C21 H26 N4 O3 . HCl

SOURCE – Zeria.

REFERENCES

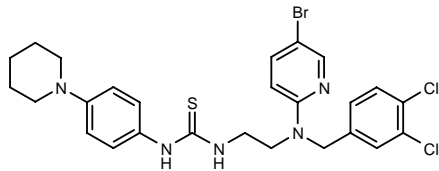
1. Nagasawa, M. et al. (Zeria Pharmaceutical Co., Ltd.) *N-Substd. benzoylamine derivs., medicines containing them and intermediates for producing them.* JP 98212271.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

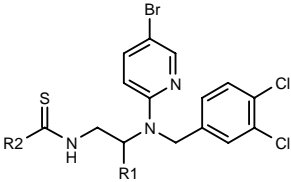
265117

1-[2-[*N*-(5-Bromopyridin-2-yl)-*N*-(3,4-dichlorobenzyl)-amino]ethyl]-3-[4-(1-piperidyl)phenyl]thiourea

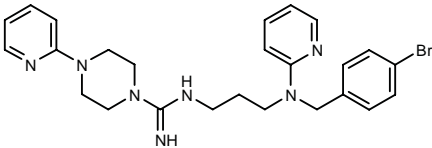


C26 H28 Br Cl2 N5 S; Mol wt: 593.4182

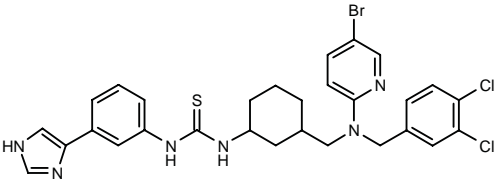
ACTION – Nonpeptide human somatostatin receptor ligand, a representative compound from a series of benzylamines, wherein the following are also specifically claimed:



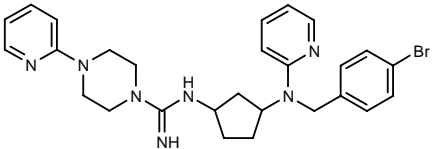
Compound	R1	R2	Formula
267724	H	1 <i>H</i> -1,2,3-triazol-4-yl-NH	C ₁₇ H ₁₆ BrCl ₂ N ₇ S
267725	H	4-(4-imidazolyl)-1-Pip	C ₂₃ H ₂₅ BrCl ₂ N ₆ S
267726	Me	4-(1-Pip)-PhNH	C ₂₇ H ₃₀ BrCl ₂ N ₅ S
267727	Et	3-(4-imidazolyl)-PhNH	C ₂₆ H ₂₅ BrCl ₂ N ₆ S



267728: C25 H30 Br N7



267729: C29 H29 Br Cl2 N6 S



267730: C27 H32 Br N7

Some compounds within the scope of the invention are reported to possess additional affinity for histamine H₃ receptors. Potentially useful for the treatment of a wide range of disorders including diabetes, tumors, growth abnormalities, autoimmune diseases, CNS disorders such as anxiety, pain and Alzheimer’s disease, diarrhea, restenosis, asthma, obesity, ulcers and pancreatitis.

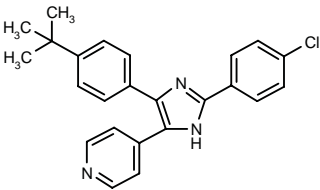
SOURCE – Novo Nordisk.

REFERENCES

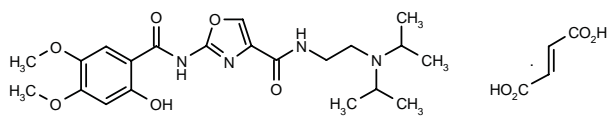
1. Ankersen, M. et al. (Novo Nordisk A/S) *Constrained somatostatin agonists and antagonists.* WO 9818786.

265503

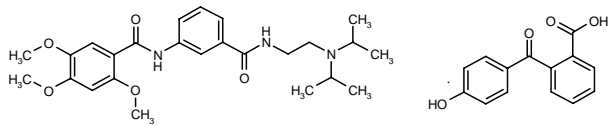
4-(*tert*-Butylphenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)-1*H*-imidazole



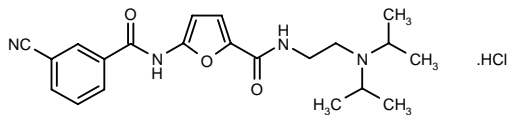
C24 H22 Cl N3; Mol wt: 387.9118



268029: C21 H30 N4 O6 . C4 H4 O4



268030: C25 H35 N3 O5 . C4 H10 O4



268031: C21 H26 N4 O3 . HCl

SOURCE – Zeria.

REFERENCES

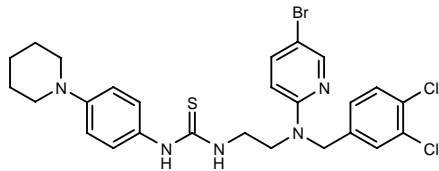
1. Nagasawa, M. et al. (Zeria Pharmaceutical Co., Ltd.) *N*-Substd. benzoylamine derivs., medicines containing them and intermediates for producing them. JP 98212271.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

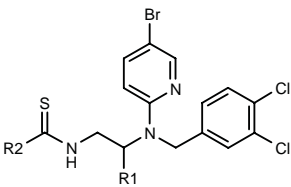
265117

1-[2-[*N*-(5-Bromopyridin-2-yl)-*N*-(3,4-dichlorobenzyl)-amino]ethyl]-3-[4-(1-piperidyl)phenyl]thiourea

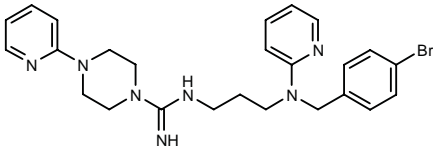


C26 H28 Br Cl2 N5 S; Mol wt: 593.4182

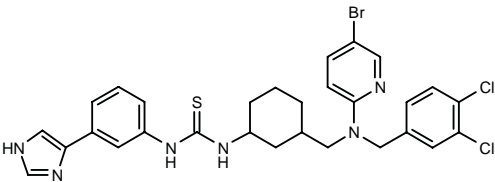
ACTION – Nonpeptide human somatostatin receptor ligand, a representative compound from a series of benzylamines, wherein the following are also specifically claimed:



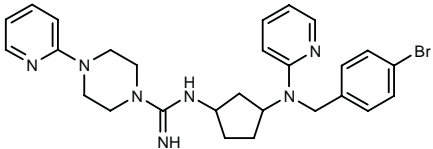
Compound	R1	R2	Formula
267724	H	1H-1,2,3-triazol-4-yl-NH	C ₁₇ H ₁₆ BrCl ₂ N ₇ S
267725	H	4-(4-imidazolyl)-1-Pip	C ₂₃ H ₂₅ BrCl ₂ N ₆ S
267726	Me	4-(1-Pip)-PhNH	C ₂₇ H ₃₀ BrCl ₂ N ₅ S
267727	Et	3-(4-imidazolyl)-PhNH	C ₂₆ H ₂₅ BrCl ₂ N ₆ S



267728: C25 H30 Br N7



267729: C29 H29 Br Cl2 N6 S



267730: C27 H32 Br N7

Some compounds within the scope of the invention are reported to possess additional affinity for histamine H₃ receptors. Potentially useful for the treatment of a wide range of disorders including diabetes, tumors, growth abnormalities, autoimmune diseases, CNS disorders such as anxiety, pain and Alzheimer’s disease, diarrhea, restenosis, asthma, obesity, ulcers and pancreatitis.

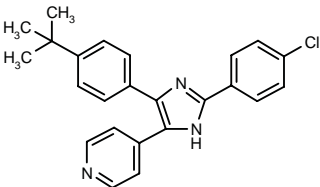
SOURCE – Novo Nordisk.

REFERENCES

1. Ankersen, M. et al. (Novo Nordisk A/S) *Constrained somatostatin agonists and antagonists*. WO 9818786.

265503

4-(*tert*-Butylphenyl)-2-(4-chlorophenyl)-5-(4-pyridyl)-1*H*-imidazole



C24 H22 Cl N3; Mol wt: 387.9118

ACTION – Glucagon receptor antagonist for the treatment of diabetes, obesity, hypertension and cachexia, able to inhibit the synthesis or activity of cytokines. A representative compound from a series of triaryl substituted imidazole derivatives.

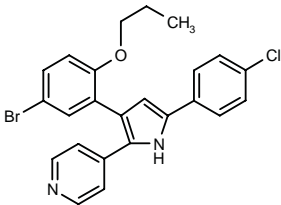
SOURCE – Merck & Co.

REFERENCES

1. Chang, L.L. (Merck & Co., Inc.) *Triaryl subst. imidazoles as glucagon antagonists*. WO 9822109.

267578

4-[3-(5-Bromo-2-propoxyphenyl)-5-(4-chlorophenyl)-1*H*-pyrrol-2-yl]pyridine



C24 H20 Br Cl N2 O; Mol wt: 467.7920

ACTION – Selective, noncompetitive, orally bioavailable human glucagon receptor (hGLUR) antagonist (IC₅₀ = 7 nM in the absence of Mg²⁺ and 170 nM in the presence of Mg²⁺) that also binds to dog and mouse GLUR but not rat, guinea pig or rabbit GLUR or other G-protein-coupled receptors; it also showed selectivity over p38 kinase (IC₅₀ = 1.44 μM). It demonstrated noncompetitive inhibition of glucagon-stimulated cAMP synthesis in CHO cells expressing the hGLUR in the presence of Mg²⁺, giving a K_b of 25 nM, with no agonist activity. The compound displayed good oral bioavailability in rats and mice. Potentially useful as a tool for elucidating the functional role of glucagon in diabetes and/or as a lead for further improvement as regards potency and selectivity.

SOURCE – Merck & Co.

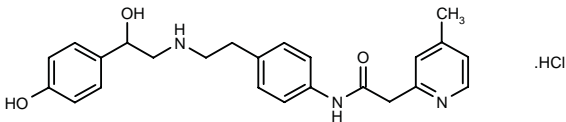
REFERENCES

1. De Laszlo, S.E. et al. (Merck & Co., Inc.) *Substd. pyridyl pyrroles, compsns. containing such cpds. and methods of use*. EP 859771, WO 9716442.

2. de Laszlo, S.E. et al. *The development of 2-pyridyl-3,5-diaryl-pyrroles as potent and selective antagonists of the human glucagon receptor*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.232.

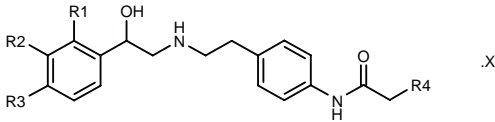
268576

N-[4-[2-[2-Hydroxy-2-(4-hydroxyphenyl)ethylamino]-ethyl]phenyl]-2-(4-methyl-2-pyridyl)acetamide hydrochloride



C24 H27 N3 O3 . HCl; Mol wt: 441.9562

ACTION – A selective β₃-adrenoceptor agonist with potential in the treatment of diabetes and obesity. A representative compound from a series of phenyl-ethanolamine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	Formula
268577	H	H	OH	2-Pyr	HCl	C ₂₃ H ₂₅ N ₃ O ₃ .HCl
268578	H	H	OH	3-Me-2-Pyr	HCl	C ₂₄ H ₂₇ N ₃ O ₃ .HCl
268579	H	OH	H	2-Pyr	HCl	C ₂₃ H ₂₅ N ₃ O ₃ .HCl
268580	OH	H	H	1-(CH ₂ Ph)-2-imidazolyl	fumarate	C ₂₈ H ₃₀ N ₄ O ₃ .C ₄ H ₄ O ₄
268581	H	H	OH	2-NH2-4-thiazolyl	.CF ₃ CO ₂ H	C ₂₁ H ₂₄ O ₃ S.C ₂ HF ₃ O ₂ .HCl
268582	H	NHCHO	OH	2-Pyr	HCl	C ₂₄ H ₂₆ N ₄ O ₄ .HCl

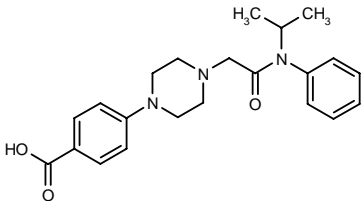
SOURCE – Yamanouchi.

REFERENCES

1. Maruyama, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel phenethanol derivs. or salts thereof*. JP 98218861.

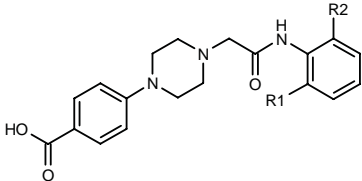
268646

4-[4-(*N*-Isopropyl-*N*-phenylcarbamoylmethyl)piperazin-1-yl]benzoic acid



C22 H27 N3 O3; Mol wt: 381.4733

ACTION – Hypoglycemic agent for the treatment of diabetes, particularly non-insulin-dependent diabetes, proven active following oral administration in a rat model of non-insulin-dependent diabetes induced by streptozotocin. Within this series of 4-(1-piperazinyl)benzoic acid derivatives, the following are also included:



Compound	R1=R2	Formula
268647	Me	C ₂₁ H ₂₅ N ₃ O ₃
268648	i-Pr	C ₂₅ H ₃₃ N ₃ O ₃

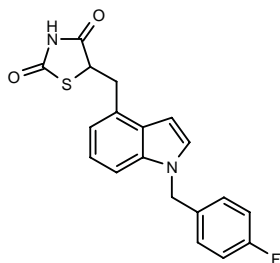
SOURCE – Merck KGaA.

REFERENCES

1. Moinet, G. et al. (Merck Patent GmbH) *New 4-(1-piperazinyl)benzoic acid derivs., process for preparing them and their therapeutic applications.* WO 9827078.

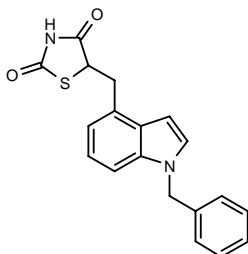
268731

5-[1-(4-Fluorobenzyl)indol-4-ylmethyl]thiazolidine-2,4-dione



C₁₉ H₁₅ F N₂ O₂ S; Mol wt: 354.4035

ACTION – Antidiabetic agent proven to enhance 2-deoxyglucose uptake in 3T3-L1 cells (280% of basal value at 50 µg/ml), while showing little toxicity (LD₅₀ > 2 g/kg p.o. in rats). Another compound from this series of thiazolidinedione derivatives is:



268732: C₁₉ H₁₆ N₂ O₂ S

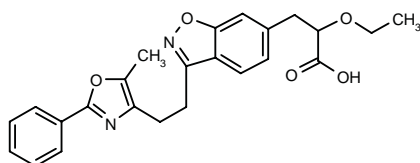
SOURCE – Senga.

REFERENCES

1. Ogawa, M. et al. (Senga Pharmaceutical Laboratory Inc.) *Thiazolidinedione derivs., method for preparing the derivs. and pharmaceutical compsns. containing same.* US 5811439.

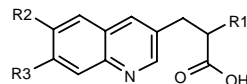
268818

2-Ethoxy-3-[3-[2-(5-methyl-2-phenyloxazol-4-yl)ethyl]-1,2-benzisoxazol-6-yl]propionic acid

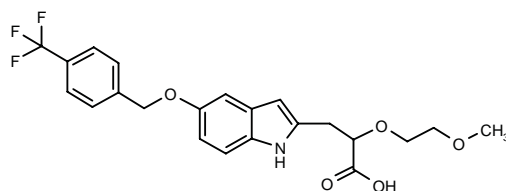


C₂₄ H₂₄ N₂ O₅; Mol wt: 420.4626

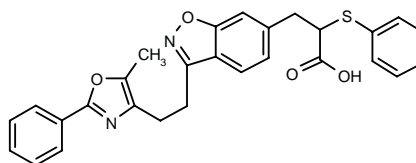
ACTION – Hypoglycemic and hypolipidemic agent proven active in KKA^y mice, where it lowered glucose and triglyceride levels to 60 and 45% of control levels, respectively, at 10 mg/kg/day p.o. x 3 days, being more potent than troglitazone (84 and 99% of control values, respectively, at 30 mg/kg/day p.o. x 3 days). Within this series of propionic acid derivatives, the following are also included:



Compound	R1	R2	R3	Formula
268819	SPh	4-CF ₃ -PhCH ₂ O	H	C ₂₆ H ₂₀ F ₃ NO ₃ S
268821	OEt	4-Cl-PhCH ₂ O	H	C ₂₁ H ₂₀ ClNO ₄
268822	OEt	H	4-Cl-PhCH ₂ O	C ₂₁ H ₂₀ ClNO ₄
268823	OPh	H	4-Cl-PhCH ₂ O	C ₂₅ H ₂₀ ClNO ₄



268820: C₂₂ H₂₂ F₃ N O₅



268824: C₂₈ H₂₄ N₂ O₄ S

SOURCE – Nippon Chemiphar.

REFERENCES

1. Nomura, Y. et al. (Nippon Chemiphar Co., Ltd.) *Propionic acid derivs.* JP 98237049, JP 98306076, WO 9828254.

CON-1

263813

Human salivary protein comprising 124 amino acids

ACTION – Human salivary protein for the treatment of diabetes and AIDS that acts by inhibition of α-glucosidase activity. Another specifically claimed glycoprotein is:

Human salivary protein comprising 82 amino acids

CON-2 [266684]

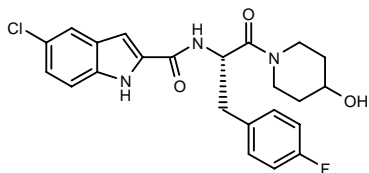
SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

REFERENCES

1. Azen, E.A. and Pan, D. (Wisconsin Alumni Research Foundation) *Human salivary proteins and fragments thereof having alpha-glucosidase inhibitory activity.* WO 9809981.

CP-320626***246964**

5-Chloro-*N*-[1(*S*)-(4-fluorobenzyl)-2-(4-hydroxypiperidin-1-yl)-2-oxoethyl]-1*H*-indole-2-carboxamide



C23 H23 Cl F N3 O3; Mol wt: 443.9037

ACTION – Antihyperglycemic agent with potential for the treatment of type II diabetes, a potent inhibitor of human liver glycogen phosphorylase (HGLPα; IC₅₀ = 205 nM against recombinant enzyme) able to block glycogenolysis in primary human hepatocytes (IC₅₀ = 1.9 μM) and *in vivo* in liver of *ob/ob* mice. The compound also potently inhibits human muscle glycogen phosphorylase (rHGLPα; IC₅₀ = 83 nM) but did not impair glycogen mobilization in muscle *in situ*. CP-320626 reduced plasma glucose levels in *ob/ob* mice for up to 10 h after single oral doses as low as 10 mg/kg, and its activity was sustained following twice-daily dosing for 2 weeks. Chronic treatment also reduced elevated plasma levels of triglycerides, cholesterol, insulin and lactate in *ob/ob* mice. No hypoglycemia or compensatory hypoglucagonemia was observed.

SOURCE – Pfizer.

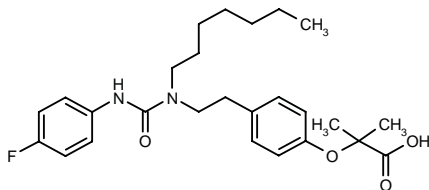
REFERENCES

1. Hulin, B. et al. (Pfizer Inc.) *Substd. N-(indole-2-carbonyl)-glycinamides and derivs. as glycogen phosphorylase inhibitors*. EP 832065, WO 9639384.
2. Hoover, D.J. et al. *Indole-2-carboxamide inhibitors of human liver glycogen phosphorylase*. J Med Chem 1998, 41(16): 2934.
3. Treadway, J.L. et al. *The human liver glycogen phosphorylase inhibitor CP-320626 shows sustained glucose lowering on multiple dosing in diabetic ob/ob mice*. Diabetes 1998, 47(Suppl. 1): Abst 1115.

*Identified compound **246964** (see **245943**) Drug Data Report 1997, 019(05): 0436.

GW-9820**267252**

2-[4-[2-[*N*³-(4-Fluorophenyl)-*N*¹-(heptyl)ureido]-ethyl]phenoxy]-2-methylpropionic acid



C26 H35 F N2 O4; Mol wt: 458.5705

ACTION – Hypoglycemic and antiobesity agent with good bioavailability that acts as a potent peroxisome proliferator-activated receptor (PPAR) ligand.

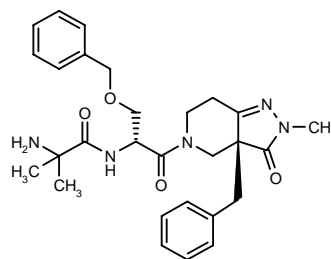
SOURCE – Glaxo Wellcome.

REFERENCES

1. Willson, T.M. (Glaxo Group Ltd.) *Use of agonists of the peroxisome proliferator activated receptor α for treating obesity*. WO 9736579.
2. Brown, P.J. et al. *Generation of secondary alkyl amines on solid support by borane reduction. Application to the parallel synthesis of PPAR ligands*. Synthesis 1997, 778.
3. Willson, T.M. *PPARs: Nuclear hormone receptors that govern glucose and lipid homeostasis*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 381.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS
CP-424391**267256****254592** (undefined isomer)*

2-Amino-*N*-[2-[3a(*R*)-benzyl-2-methyl-3-oxo-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-5-yl]-1(*R*)-(benzyloxymethyl)-2-oxoethyl]isobutyramide



C28 H35 N5 O4; Mol wt: 505.6155

ACTION – Growth hormone (GH) secretagogue under development for use in conditions associated with musculoskeletal frailty. It gave an EC₅₀ value of 3 nM in the *in vitro* rat pituitary cell assay and ED₅₀s of 0.04 mg/kg i.v. and 0.3 mg/kg p.o., respectively, for stimulation of GH secretion in rats and beagle dogs. Pharmacokinetics in rats and dogs were characterized by moderate systemic clearance and volume of distribution, short half-life (1.3 h in dogs) and good oral bioavailability (44% in dogs, 65% in rats).

SOURCE – Pfizer.

REFERENCES

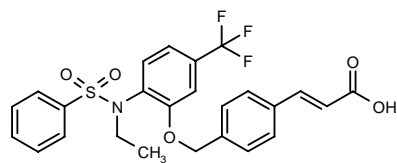
1. Carpino, P.A. et al. (Pfizer Inc.) *Growth-hormone secretagogues*. EP 869968, WO 9724369.
2. Carpino, P.A. et al. *Design, synthesis and biological evaluation of a novel series of pyrazolidone-piperidine growth hormone secretagogues*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 276.
3. Zawistoski, M.P. et al. *The total synthesis of the growth hormone secretagogue CP-424,391-18, utilizing a retro-mannich re-arrangement and resolution of the key pyrazolonepiperidine intermediate*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 165.

*See **254135** Drug Data Report 1997, 019(10): 0914.

UTERINE STIMULANTS
AND TOCOLYTICS

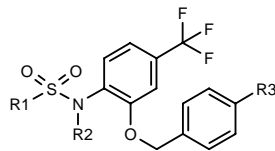
268235

3-[4-[2-[N-Ethyl-N-(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl]phenyl]-2(E)-propenoic acid



C25 H22 F3 N O5 S; Mol wt: 505.5108

ACTION – Agent with high affinity for the prostaglandin E₂ (PGE₂) EP₁ receptor (K_i = 0.0002 μM against [³H]-PGE₂ binding in CHO cells expressing murine EP₁ receptors) and low toxicity. Potentially useful for inhibiting or inducing uterine contractions, inhibiting or promoting digestive tract motility, inducing analgesia and sleep, suppressing gastric acid secretion, lowering blood pressure or inducing diuresis. Other compounds from this series of sulfonamide and carboxamide derivatives include the following:



Compound	R1	R2	R3	Formula
268236	Ph	cyclopentyl	CO2H	C ₂₆ H ₂₄ F ₃ NO ₅ S
268237	2-furyl	i-Bu	CH=CHCO2H	C ₂₅ H ₂₄ F ₃ NO ₆ S
268238	Ph	i-Pr	OCH2CO2H	C ₂₅ H ₂₄ F ₃ NO ₆ S
268239	Ph	i-Pr	ethynylene-CO2H	C ₂₆ H ₂₂ F ₃ NO ₅ S

SOURCE – Ono.

REFERENCES

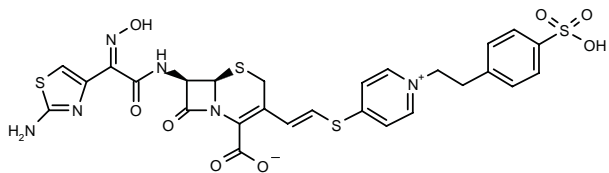
1. Ohuchida, S. and Nagao, Y. (Ono Pharmaceutical Co., Ltd.) *Sulfonamide and carboxamide derivs. and drugs containing the same as the active ingredient*. WO 9827053.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

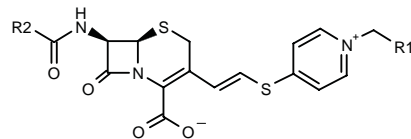
267888

(6*R*,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(hydroxyimino)-acetamido]-3-[2-[1-[2-(4-sulfo-phenyl)ethyl]-pyridinium-4-ylsulfany]vinyl]-3-cephem-4-carboxylate



C27 H24 N6 O8 S4; Mol wt: 688.7846

ACTION – Cephem antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P, methicillin-resistant *S. aureus* 92-1044, *Enterococcus faecalis* ATCC-21212 and *Escherichia coli* NIHJ JC-2 (MIC = 0.39, 6.25, 0.39 and 0.0125 μg/ml, respectively, vs. 0.2, > 100, 100 and 0.05 μg/ml, respectively, for flomoxef). Other compounds from this series of cephem derivatives include the following:



Compound	R1	R2	Formula
267889	CH2SO3H	2-NH2-4-thiazolyl-C(=NOH)	C ₂₁ H ₂₀ N ₆ O ₈ S ₄
267890	2-F-4-SO3H-Ph	2-NH2-4-thiazolyl-C(=NOH)	C ₂₆ H ₂₁ FN ₆ O ₈ S ₄
267891	2-CF3-4-SO3H-Ph	2-NH2-4-thiazolyl-C(=NOH)	C ₂₇ H ₂₁ F ₃ N ₆ O ₈ S ₄
267892	CH2SO3H	2-thienyl-CH2	C ₂₂ H ₂₁ N ₃ O ₇ S ₄

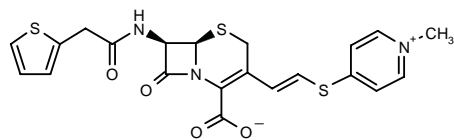
SOURCES – Otsuka; Taiho.

REFERENCES

1. Akagi, H. et al. (Otsuka Pharmaceutical Co., Ltd.;Taiho Pharmaceutical Co., Ltd.) *Novel cephem cpds*. JP 98182655.

267893

(6*R*,7*R*)-3-[2-(1-Methylpyridinium-4-ylsulfany]vinyl]-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate

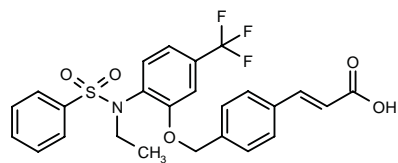


C21 H19 N3 O4 S3; Mol wt: 473.5961

UTERINE STIMULANTS
AND TOCOLYTICS

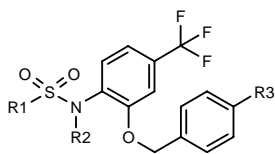
268235

3-[4-[2-[N-Ethyl-N-(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl]phenyl]-2(E)-propenoic acid



C25 H22 F3 N O5 S; Mol wt: 505.5108

ACTION – Agent with high affinity for the prostaglandin E₂ (PGE₂) EP₁ receptor (K_i = 0.0002 μM against [³H]-PGE₂ binding in CHO cells expressing murine EP₁ receptors) and low toxicity. Potentially useful for inhibiting or inducing uterine contractions, inhibiting or promoting digestive tract motility, inducing analgesia and sleep, suppressing gastric acid secretion, lowering blood pressure or inducing diuresis. Other compounds from this series of sulfonamide and carboxamide derivatives include the following:



Compound	R1	R2	R3	Formula
268236	Ph	cyclopentyl	CO2H	C ₂₆ H ₂₄ F ₃ NO ₅ S
268237	2-furyl	i-Bu	CH=CHCO2H	C ₂₅ H ₂₄ F ₃ NO ₆ S
268238	Ph	i-Pr	OCH2CO2H	C ₂₅ H ₂₄ F ₃ NO ₆ S
268239	Ph	i-Pr	ethynylene-CO2H	C ₂₆ H ₂₂ F ₃ NO ₅ S

SOURCE – Ono.

REFERENCES

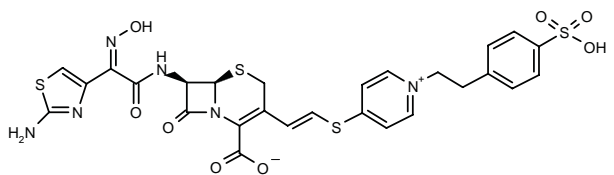
1. Ohuchida, S. and Nagao, Y. (Ono Pharmaceutical Co., Ltd.) *Sulfonamide and carboxamide derivs. and drugs containing the same as the active ingredient*. WO 9827053.

ANTIINFECTIVE THERAPY

β-LACTAM ANTIBIOTICS

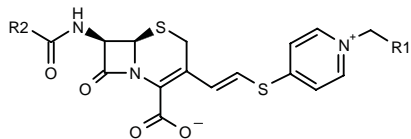
267888

(6*R*,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2(*Z*)-(hydroxyimino)-acetamido]-3-[2-[1-[2-(4-sulfophenyl)ethyl]-pyridinium-4-ylsulfany]vinyl]-3-cephem-4-carboxylate



C27 H24 N6 O8 S4; Mol wt: 688.7846

ACTION – Cephem antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* FDA 209P, methicillin-resistant *S. aureus* 92-1044, *Enterococcus faecalis* ATCC-21212 and *Escherichia coli* NIHJ JC-2 (MIC = 0.39, 6.25, 0.39 and 0.0125 μg/ml, respectively, vs. 0.2, > 100, 100 and 0.05 μg/ml, respectively, for flomoxef). Other compounds from this series of cephem derivatives include the following:



Compound	R1	R2	Formula
267889	CH2SO3H	2-NH2-4-thiazolyl-C(=NOH)	C ₂₁ H ₂₀ N ₆ O ₈ S ₄
267890	2-F-4-SO3H-Ph	2-NH2-4-thiazolyl-C(=NOH)	C ₂₆ H ₂₁ FN ₆ O ₈ S ₄
267891	2-CF3-4-SO3H-Ph	2-NH2-4-thiazolyl-C(=NOH)	C ₂₇ H ₂₁ F ₃ N ₆ O ₈ S ₄
267892	CH2SO3H	2-thienyl-CH2	C ₂₂ H ₂₁ N ₃ O ₇ S ₄

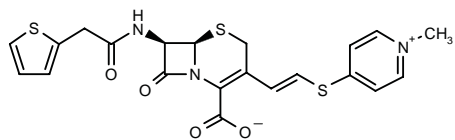
SOURCES – Otsuka; Taiho.

REFERENCES

1. Akagi, H. et al. (Otsuka Pharmaceutical Co., Ltd.;Taiho Pharmaceutical Co., Ltd.) *Novel cephem cpds*. JP 98182655.

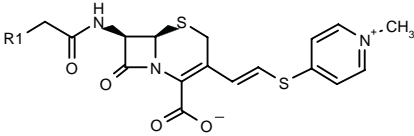
267893

(6*R*,7*R*)-3-[2-(1-Methylpyridinium-4-ylsulfany]vinyl]-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate



C21 H19 N3 O4 S3; Mol wt: 473.5961

ACTION – Cephem antibiotic active *in vitro* against Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) strains. Compound exhibited MIC values of 0.05, 0.78, 0.05, 0.39 and 1.56 µg/ml, respectively, when tested against *S. aureus* FDA 209P, MRSA 92-1044, *Staphylococcus epidermidis* ATCC-12228, *Enterococcus faecalis* ATCC-21212 and *Escherichia coli* NIHJ JC-2; respective MIC values for flomoxef were 0.2, > 100, 0.78, 100 and 0.05 µg/ml. *In vivo*, compound was found to be effective against MRSA 92-1191 infections in mice (ED₅₀ = 3.27 mg/kg), whereas flomoxef and imipenem where inactive (ED₅₀ > 100 mg/kg). Other compounds from this series of cephem derivatives include the following:



Compound	R1	Formula
267894	Ph	C ₂₃ H ₂₁ N ₃ O ₄ S ₂
267895	3-thienyl	C ₂₁ H ₁₉ N ₃ O ₄ S ₃
267896	4-thiazolyl	C ₂₀ H ₁₈ N ₄ O ₄ S ₃

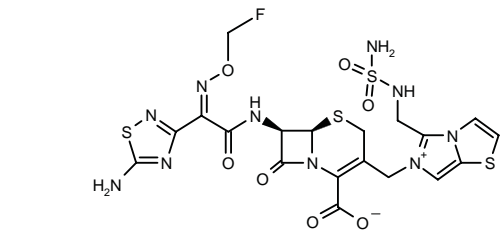
SOURCES – Otsuka; Taiho.

REFERENCES

1. Akagi, H. et al. (Otsuka Pharmaceutical Co., Ltd.;Taiho Pharmaceutical Co., Ltd.) *Cephem cpds.* JP 98182656.

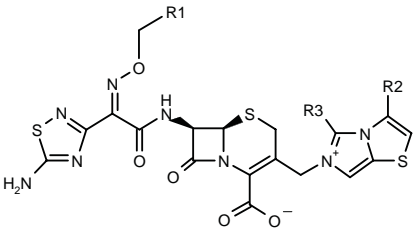
268049

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(fluoromethoxy-imino)acetamido]-3-[5-(sulfamoylaminomethyl)-imidazo-[5,1-*b*]thiazolium-6-ylmethyl]-3-cephem-4-carboxylate

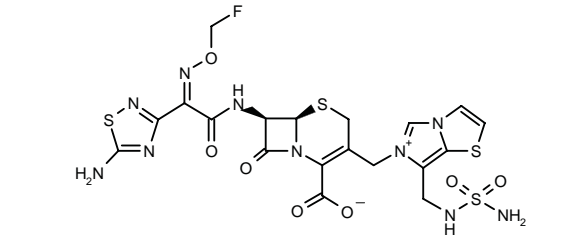


C19 H19 F N10 O7 S4; Mol wt: 646.6841

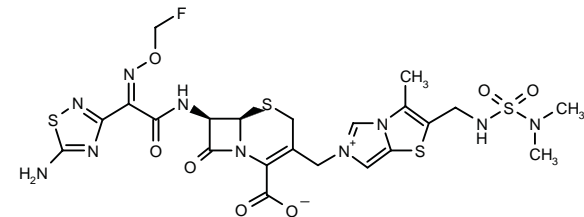
ACTION – Cephem antibiotic with broad-spectrum activity against Gram-positive and Gram-negative bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and imipenem-resistant *Pseudomonas aeruginosa*. Compound showed MIC values of 6.25, 0.05 and 3.13 µg/ml against MRSA 126, PRSP JPR 20 and imipenem-resistant *P. aeruginosa* PA01, respectively. Other exemplified cephem derivatives include the following:



Compound	R1	R2	R3	Formula
268050	F	CH2NH-SO2NH2	H	C ₁₉ H ₁₉ FN ₁₀ O ₇ S ₄
268051	CH2F	CH2NH-SO2NH2	H	C ₂₀ H ₂₁ FN ₁₀ O ₇ S ₄
268052	F	CH2CH2NH-SO2NH2	H	C ₂₀ H ₂₁ FN ₁₀ O ₇ S ₄
268053	H	H	CH2NH-SO2NH2	C ₁₉ H ₂₀ N ₁₀ O ₇ S ₄
268054	Me	H	CH2NH-SO2NH2	C ₂₀ H ₂₂ N ₁₀ O ₇ S ₄
268055	F	H	(<i>R</i>)-CH(Me)-NHSO2NH2	C ₂₀ H ₂₁ FN ₁₀ O ₇ S ₄
268056	F	H	(<i>S</i>)-CH(Me)-NHSO2NH2	C ₂₀ H ₂₁ FN ₁₀ O ₇ S ₄
268059	F	H	(<i>R</i>)-CH(Me)-NHSO2N(Me)2	C ₂₂ H ₂₅ FN ₁₀ O ₇ S ₄
268060	F	H	CH2N(Me)-SO2NH2	C ₂₀ H ₂₁ FN ₁₀ O ₇ S ₄



268057: C19 H19 F N10 O7 S4



268058: C22 H25 F N10 O7 S4

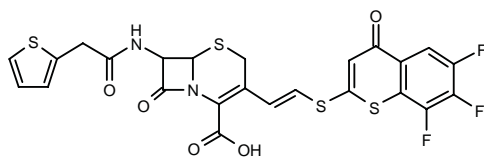
SOURCE – Meiji Seika.

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1. Kobayashi, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel cephem derivs.* WO 9825935.

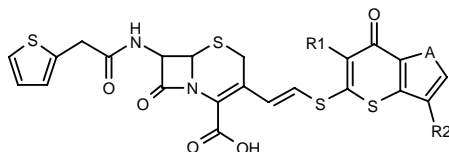
268803

7-[2-(2-Thienyl)acetamido]-3-[2-(6,7,8-trifluoro-4-oxo-4*H*-1-benzothiopyran-2-ylsulfanyl)vinyl]-3-cephem-4-carboxylic acid

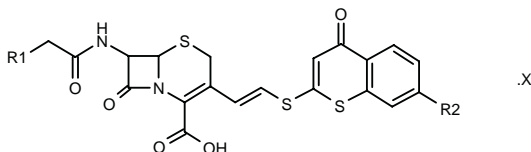


C24 H15 F3 N2 O5 S4; Mol wt: 596.6495

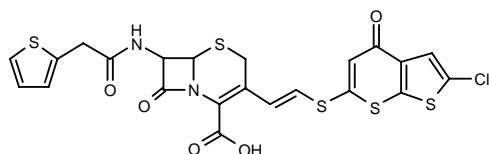
ACTION – Cephem antibiotic proven active *in vitro* against *Staphylococcus aureus* FDA 209P (MIC = 0.025 µg/ml), *Enterococcus faecalis* NCTC-12201 (MIC = 0.78 µg/ml) and methicillin-resistant *S. aureus* (MRSA; MIC₈₀ = 3.13 µg/ml), being more potent than flomoxef (0.20, > 100 and 100 µg/ml, respectively) and vancomycin (0.78, > 1000 and 1.56 µg/ml, respectively). A representative compound from a series of cepheems, wherein the following are also included:



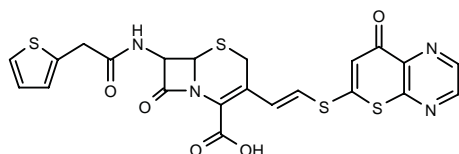
Compound	R1	R2	A	Formula
268805	H	H	-O-	C ₂₂ H ₁₈ N ₂ O ₆ S ₄
268806	H	H	-S-	C ₂₂ H ₁₈ N ₂ O ₅ S ₅
268810	Br	H	-S-	C ₂₂ H ₁₅ BrN ₂ O ₅ S ₅
268811	H	NO2	-S-	C ₂₂ H ₁₅ N ₃ O ₇ S ₅



Compound	R1	R2	X	Formula
268808	2-thienyl	1-Pip	HCl	C ₂₉ H ₂₇ N ₅ O ₅ S ₄ ·HCl
268812	Ph	H		C ₂₆ H ₂₀ N ₂ O ₅ S ₃
268813	2-thienyl	CH2S-C(=NH)NH2	HCO2H	C ₂₆ H ₂₂ N ₄ O ₅ S ₅ ·HCO ₂ H
268814	2-thienyl	H		C ₂₄ H ₁₈ N ₂ O ₅ S ₄



268807: C22 H15 Cl N2 O5 S5



268809: C22 H16 N4 O5 S4

SOURCE – Zenyaku Kogyo.

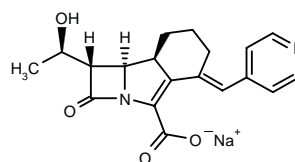
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265494

(1*S*,8*aS*,8*bR*)-1-[1(*R*)-Hydroxyethyl]-2-oxo-5(*E*)-(4-pyridylmethylene)-1,2,5,6,7,8,8*a*,8*b*-octahydroazeto-[2,1-*a*]isoindole-4-carboxylic acid sodium salt

(8*S*,9*R*,10*S*)-10-[1(*R*)-Hydroxyethyl]-11-oxo-4(*E*)-(4-pyridylmethylene)-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic acid sodium salt



C19 H19 N2 Na O4; Mol wt: 362.3591

ACTION – Tricyclic carbapenem (trinem) antibiotic active against Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE) (MIC₉₀ = 4 and 2 µg/ml, respectively). No toxicity was observed in rats at doses up to 1000 mg/kg p.o.

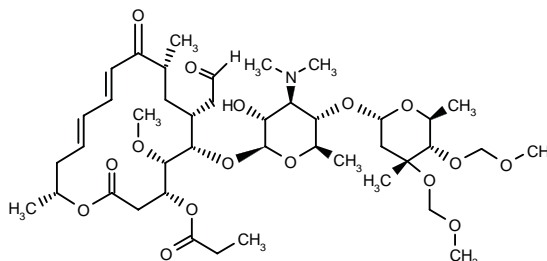
SOURCE – Glaxo Wellcome.

REFERENCES

1. Rossi, T. et al. (Glaxo Wellcome SpA) *Tricyclic carbapenem cpds.* WO 9821210.

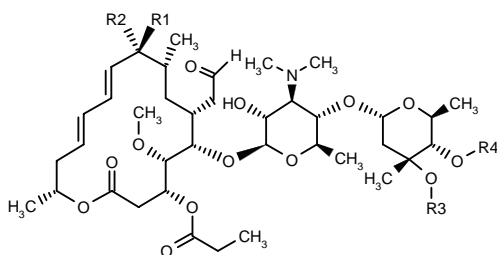
MISCELLANEOUS ANTIBIOTICS**267897**

[3*R*-(3α,4β,5α,6α,8α,10*E*,12*E*,15α)]-5-[3,6-Dideoxy-3-(dimethylamino)-4-*O*-[6-deoxy-3-*O*,4-*O*-bis(methoxymethyl)-3-*C*-methyl-α-*L*-mannopyranosyl]-β-*D*-glucopyranosyloxy]-6-(formylmethyl)-4-methoxy-8-methyl-9-oxo-3-(propionyloxy)hexadeca-10,12-dieno-15-lactone



C42 H69 N O16; Mol wt: 843.9981

ACTION – Antibacterial agent tested *in vitro* against *Staphylococcus aureus* 209P JC-1, *Micrococcus luteus* ATCC9341, *Enterococcus faecalis* W-73, *Streptococcus pneumoniae* IP692 and *Streptococcus pneumoniae* type I (MIC = 6.25, 0.78, 12.50, 0.78 and 0.78 µg/ml, respectively). Other compounds from this series of 16-membered cyclic macrolide derivatives include the following:



Compound	R1	R2	R3	R4	Formula
267898	OCH ₂ OEt	H	H	COEt	C ₄₄ H ₇₃ NO ₁₆
267899	-O-		H	CH ₂ OMe	C ₄₀ H ₆₅ NO ₁₅
267900	-O-		H	CH ₂ OEt	C ₄₁ H ₆₇ NO ₁₅
267901	-O-		CH ₂ OEt	CH ₂ OEt	C ₄₄ H ₇₃ NO ₁₆

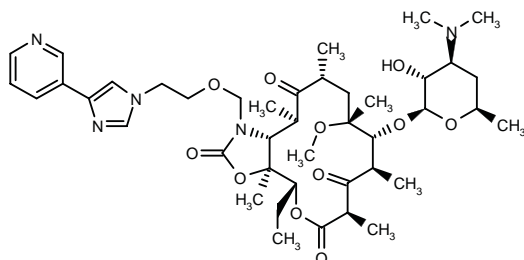
SOURCE – Meiji Seika.

REFERENCES

1. Omoto, S. et al. (Meiji Seika Kaisha, Ltd.) *Novel 16-membered cyclic macrolide derivs.* JP 98182690.

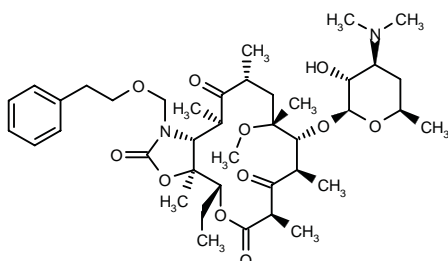
268259

11-Desoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[2-[4-(3-pyridyl)imidazol-1-yl]ethoxymethylamino]-3-oxoerythromycin A *N*¹¹,*O*¹²-cyclic carbamate



C42 H63 N5 O11; Mol wt: 813.9837

ACTION – Antibacterial agent, an erythromycin derivative with particularly potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.08 µg/ml), *Staphylococcus epidermidis* 012GO111 (MIC = 0.08 µg/ml), *Streptococcus pyogenes* 02A1UC1 (MIC = 0.02 µg/ml or less), *Streptococcus agalactiae* 02B1HT1 (MIC = 0.02 µg/ml or less), *Streptococcus faecalis* 02D2UC1 (MIC = 0.02 µg/ml or less) and *Streptococcus pneumoniae* 032UC1 (MIC = 0.02 µg/ml or less). Also reported to be active against *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, *Ureaplasma*, *Toxoplasma* and *Mycobacterium*. Another compound from this series of erythromycin derivatives is:



268260: C40 H62 N2 O11

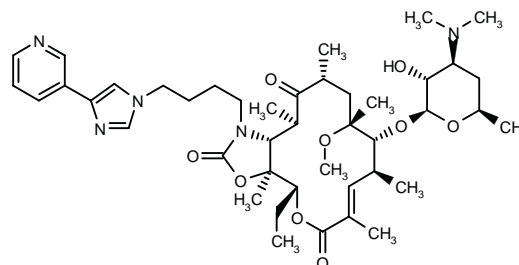
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Auger, J.-M. et al. (Hoechst Marion Roussel, SA) *Novel erythromycin derivs., method for preparing them and their use as medicine.* WO 9825942.

268681

11-Desoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-11-[4-[4-(3-pyridyl)imidazol-1-yl]butylamino]-2,3-didehydro-erythromycin A *N*¹¹,*O*¹²-cyclic carbamate



C43 H65 N5 O9; Mol wt: 796.0125

ACTION – Antibacterial agent, an erythromycin derivative with particularly potent activity against Gram-positive bacteria such as *Staphylococcus aureus* 011UC4 (MIC = 0.08 µg/ml), *Staphylococcus epidermidis* 012GO111 (MIC = 0.15 µg/ml), *Streptococcus pyogenes* 02A1UC1 (MIC = 0.02 µg/ml or less), *Streptococcus agalactiae* 02B1HT1 (MIC = 0.02 µg/ml or less), *Streptococcus faecalis* 02D2UC1 (MIC = 0.02 µg/ml or less) and *Streptococcus pneumoniae* 030ROli (MIC = 0.02 µg/ml or less). Compound also showed antibacterial activity against certain strains of *Haemophilus influenzae*, and is reported to be also useful against infections caused by *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella*, *Ureaplasma*, *Toxoplasma* and *Mycobacterium*.

SOURCE – Hoechst Marion Roussel.

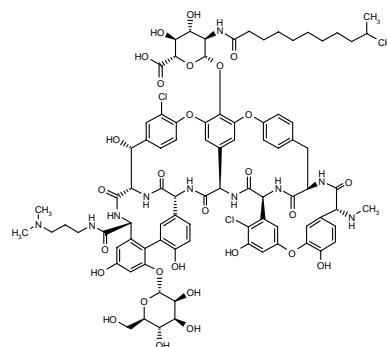
REFERENCES

1. Agouridas, C. and Chantot, J.-F. (Hoechst Marion Roussel, SA) *Novel erythromycin derivs., method of preparation and application as medicines.* WO 9828316.

BI-397

264176

5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-(10-methylundecanamido)-β-D-glucopyranosyl]-38-[*N*-[3-(dimethylamino)propyl]carbamoil]-42-*O*-α-D-mannopyranosyl-*N*¹⁵-methylristomycin A aglycone



C88 H100 Cl2 N10 O28; Mol wt: 1816.7060

ACTION – Semisynthetic parenteral glycopeptide antibiotic shown to be more active than vancomycin or teicoplanin against coagulase-positive or -negative staphylococci including methicillin-resistant strains with poor susceptibility or resistant to teicoplanin; it was also more active than vancomycin against streptococci including penicillin-resistant strains of *Streptococcus pneumoniae*, and more active than teicoplanin against vancomycin-susceptible and -resistant strains of *VanB* enterococci. As evaluated in several animal models of infection such as staphylococcal, streptococcal and enterococcal septicemia in immunocompetent and neutropenic mice and staphylococcal endocarditis in rats, it was also more potent than reference compounds. Pharmacokinetic studies in various animal species indicated the feasibility of once-daily administration in humans, and it was better tolerated than vancomycin in rats and dogs.

SOURCES – Biosearch Italia; Versicor.

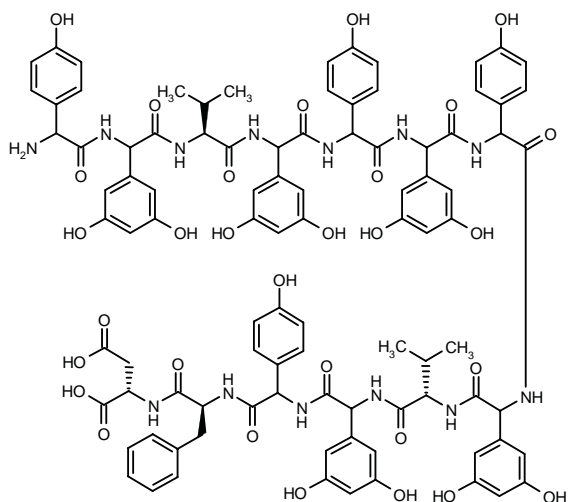
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1. Malabarba, A. et al. *BI 397: A new developmental semisynthetic glycopeptide antibiotic*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-107.
2. *Biosearch Italia and Versicor establish infectious disease collaboration*. Prous Science Daily Essentials 1998, Feb 25.
3. *Company Profile: Versicor*. Prous Science Daily Essentials 1998, Nov 3.

FEGLYMYCINE

265439

D,L-[2-(4-Hydroxyphenyl)]glycyl-D,L-[2-(3,5-dihydroxyphenyl)]glycyl-L-valyl-D,L-[2-(3,5-dihydroxyphenyl)]glycyl-D,L-[2-(4-hydroxyphenyl)]glycyl-D,L-[2-(3,5-dihydroxyphenyl)]glycyl-D,L-[2-(4-hydroxyphenyl)]glycyl-D,L-[2-(3,5-dihydroxyphenyl)]glycyl-L-valyl-D,L-[2-(3,5-dihydroxyphenyl)]glycyl-D,L-[2-(4-hydroxyphenyl)]glycyl-L-phenylalanyl-L-aspartic acid



C95 H97 N13 O30; Mol wt: 1900.8720

ACTION – Antibiotic isolated from the microorganism *Streptomyces* HAG 4675 (DSM 11171), active against Gram-positive bacteria such as *Staphylococcus aureus* SG511 (MIC = 64 µg/ml) and *Streptococcus pyogenes* 77A (MIC = 32 µg/ml).

SOURCE – Hoechst Marion Roussel.

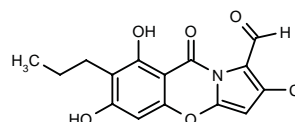
REFERENCES

1. Vértessy, L. et al. (Hoechst AG) *New antibiotic, feclymycin, process for its preparation and use of the same*. EP 848064, JP 98204099.

MISCELLANEOUS ANTIBACTERIAL DRUGS

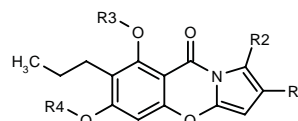
268044

2-Chloro-6,8-dihydroxy-9-oxo-7-propyl-9H-pyrrolo[2,1-b]-[1,3]benzoxazine-1-carbaldehyde



C15 H12 Cl N O5; Mol wt: 321.7148

ACTION – Antibacterial agent active against Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus* 29213 (MIC = 4.0 µg/ml) and *Escherichia coli* B90 (MIC = 4.0 µg/ml). Within this series of 4-oxo-1,3-benzoxazine derivatives, the following are also included:



Compound	R1	R2	R3=R4	Formula
268045	H	H	H	C ₁₄ H ₁₃ NO ₄
268046	Cl	CH=NOH	H	C ₁₅ H ₁₃ ClN ₂ O ₅
268047	Cl	H	Ac	C ₁₈ H ₁₆ ClNO ₆

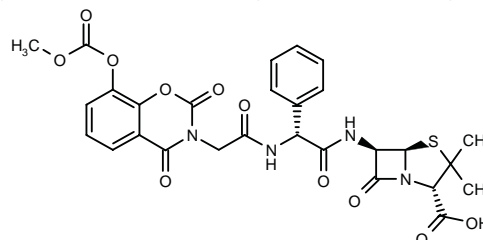
SOURCE – Warner-Lambert.

REFERENCES

1. Domagala, J.M. et al. (Warner-Lambert Co.) *Antibacterial agents*. WO 9825932.

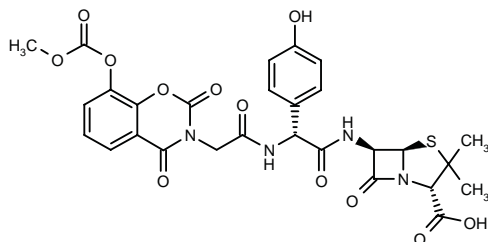
268573

(3S,5R,6R)-6-[2(R)-[2-[8-(Methoxycarbonyloxy)-2,4-dioxo-3,4-dihydro-2H-1,3-benzoxazin-3-yl]acetamido]-2-phenylacetamido]-2,2-dimethylpenam-3-carboxylic acid



C28 H26 N4 O11 S; Mol wt: 626.5964

ACTION – Antibacterial agent, a conjugate of ampicillin with a benzoxazinedione with improved antimicrobial activity against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Klebsiella*. Another compound from this series of benzoxazinedione–antibiotic conjugates is:



268574: C28 H26 N4 O12 S

SOURCE – Grünenthal.

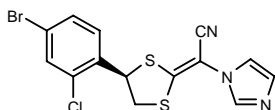
REFERENCES

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ANTIFUNGAL AGENTS

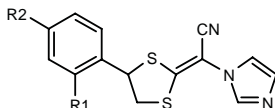
268377

(*E*)-2-[4(*R*)-(4-Bromo-2-chlorophenyl)-1,3-dithiolan-2-ylidene]-2-(1-imidazolyl)acetonitrile



C14 H9 Br Cl N3 S2; Mol wt: 398.7351

ACTION – Antifungal agent with high *in vitro* activity against *Trichophyton mentagrophytes* IFO 5811 and TIMM 2789 (MIC = 0.02 and 0.01 µg/ml, respectively) and *Trichophyton rubrum* IFO 6204 and IFO 5805 (MIC = 0.01 and 0.01 µg/ml, respectively). Other compounds from this series of optically active 4-phenyl-1,3-dithiolane derivatives include the following:



Compound	R1	R2	Isomer	Formula
268378	H	Br	R	C ₁₄ H ₁₀ BrN ₃ S ₂
268379	H	Br	RS	C ₁₄ H ₁₀ BrN ₃ S ₂
268380	H	Cl	R	C ₁₄ H ₁₀ ClN ₃ S ₂
268381	H	Cl	RS	C ₁₄ H ₁₀ ClN ₃ S ₂
268382	F	H	R	C ₁₄ H ₁₀ FN ₃ S ₂
268383	Br	H	R	C ₁₄ H ₁₀ BrN ₃ S ₂
268384	Br	H	RS	C ₁₄ H ₁₀ BrN ₃ S ₂

SOURCE – Nihon Nohyaku.

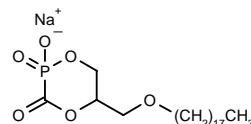
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ANTIVIRAL DRUGS

268048

2-Hydroxy-5-(octadecyloxymethyl)-1,4,2λ⁵-dioxaphosphorinan-3-one 2-oxide sodium salt



C22 H42 Na O6 P; Mol wt: 456.5318

ACTION – Antiviral agent especially useful for the treatment of human herpesvirus infections and human retrovirus infections (HIV). A particularly preferred compound within a series of phosphonoformic acid derivatives.

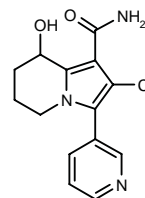
SOURCE – Astra.

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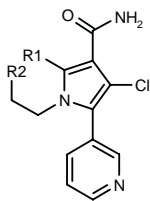
268226

2-Chloro-8-hydroxy-3-(3-pyridyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide



C14 H14 Cl N3 O2; Mol wt: 291.7366

ACTION – Antiviral agent for the treatment of infections caused by viruses of the herpes family such as herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), HHV-7, HHV-8 and Epstein-Barr virus (EBV). Antiviral activity was demonstrated *in vitro* against human cytomegalovirus strains AD-169 (IC₅₀ = 0.02-0.2 µg/ml) and Davis (IC₅₀ = 0.015-0.027 µg/ml). In addition, the compound exhibits anti-TNF-α activity, as demonstrated by inhibition of HIV reactivation induced by TNF-α or PMA in U1 cells, and thus may be used for the treatment of TNF-mediated diseases such as inflammation, asthma, diabetes, cachexia, gastrointestinal disorders such as Crohn's disease, CNS disorders, immune disorders, ischemia/reperfusion injury, HIV infection and tuberculosis. Within this series of specifically claimed pyrrole derivatives, the following are also included:



Compound	R1,R2	Formula
268227	-CH=CH-	C ₁₄ H ₁₂ ClN ₃ O
268228	-CH(OMe)CH2-	C ₁₅ H ₁₆ ClN ₃ O ₂
268229	-CH=C(OMe)-	C ₁₅ H ₁₄ ClN ₃ O ₂
268230	-CH=C(Cl)-	C ₁₄ H ₁₁ Cl ₂ N ₃ O

SOURCE – Rhône-Poulenc Rorer.

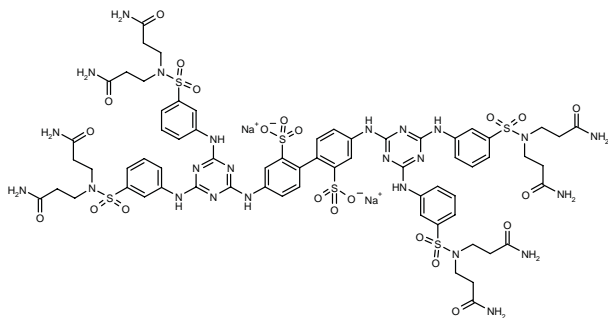
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CL-387626

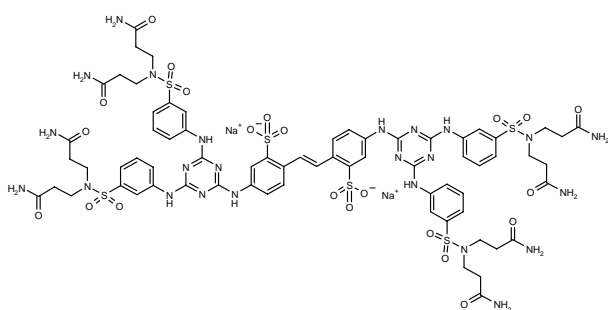
266287

4,4'-Bis[4,6-bis[3-[bis(3-amino-3-oxopropyl)aminosulfonyl]phenylamino]-1,3,5-triazin-2-ylamino][1,1'-biphenyl]-2,2'-disulfonic acid disodium salt



C66 H76 N24 Na2 O22 S6; Mol wt: 1795.8480

ACTION – Antiviral agent for human respiratory syncytial virus (RSV) that appears to target viral fusion but not attachment and whose site of action appears to be the 70K viral fusion glycoprotein. It was shown to be highly potent and selective against human RSV, giving IC₅₀ values of 0.05, 18.5 and > 25 µM, respectively, against RSV, human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1). The following lead compound was somewhat less active:



266286: C68 H78 N24 Na2 O22 S6

SOURCE – Wyeth-Ayerst.

REFERENCES

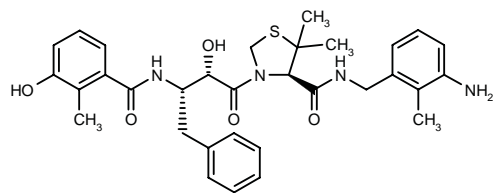
1. Gluzman, Y. et al. (American Cyanamid Co.) *Bis-aryloxy(amino)-triazinyl-oxy(amino)aryl derivs., their preparation and their use as antiviral agents.* CA 2197393, EP 795549, JP 97309882, US 5852015.

2. Ding, W.-D. et al. *Novel and specific respiratory syncytial virus inhibitors that target virus fusion.* J Med Chem 1998, 41(15): 2671.

AIDS MEDICINES

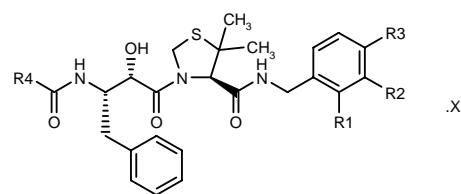
267829

N-(3-Amino-2-methylbenzyl)-3-[2(S)-hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutyryl]-5,5-dimethylthiazolidine-4(R)-carboxamide



C32 H38 N4 O5 S; Mol wt: 590.7412

ACTION – Antiviral agent for AIDS with HIV protease-inhibitory activity (89.5% inhibition at 50 nM). Within this series of dipeptide derivatives, the following are also included:



Compound	R1	R2	R3	R4	X	Formula
267830	H	NH2	H	2-Me-3-OH-Ph		C ₃₁ H ₃₆ N ₄ O ₅ S
267831	H	H	NH2	2-Me-3-OH-Ph		C ₃₁ H ₃₆ N ₄ O ₅ S
267832	Me	NH2	H	2,6-(Me)2-PhOCH2	HCl	C ₃₄ H ₄₂ N ₄ O ₅ S.HCl

SOURCE – Japan Energy.

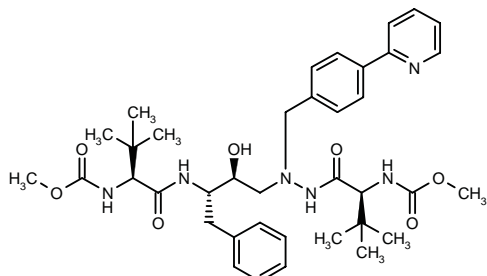
REFERENCES

1. Nojima, S. et al. (Japan Energy Corp.) *Novel dipeptide cpds. or their pharmaceutically acceptable salt and their use.* JP 98182601.

BMS-232632***257722**

N'-[2(*S*)-Hydroxy-3(*S*)-[*N*-(methoxycarbonyl)-*L*-*tert*-leucylamino]-4-phenylbutyl]-*N*^α-(methoxycarbonyl)-*N'*-[4-(2-pyridyl)benzyl]-*L*-*tert*-leucylhydrazide

CGP-73547



C38 H52 N6 O7; Mol wt: 704.8638

M.p. 207-9 °C.

ACTION – Potent, orally active azapeptide HIV protease inhibitor ($K_i = 1$ nM) with potent anti-HIV-1 activity against a range of isolates in cell culture ($EC_{50} = 2.1$ -5.3 nM; $EC_{90} = 7$ -10 nM); it is more potent than any other approved HIV protease inhibitor, even in the presence of human serum, and it selects for resistant variants less readily than nelfinavir or zidovudine. The compound has good oral bioavailability in rats (15-25%), dogs (25-63%) and man. In humans, plasma concentrations exceeded EC_{50} values for over 24 h following single oral doses of 300 mg or more and doses of up to 1200 mg were well tolerated.

SOURCES – Bristol-Myers Squibb; Novartis.

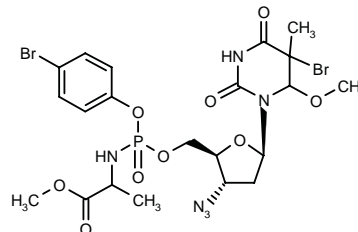
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2. Bold, G. et al. *New aza-dipeptide analogues as potent and orally absorbed HIV-1 protease inhibitors: Candidates for clinical development.* J Med Chem 1998, 41(18): 3387.
3. Gong, Y.-F. et al. *Antiviral activity and resistance profile of an HIV-1 protease inhibitor BMS-232632.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-79.
4. O'Mara, E.M. et al. *BMS-232632: Single-oral dose-safety and pharmacokinetic study in healthy volunteers.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-242.
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6. *Bristol-Myers Squibb expands protease inhibitor research.* Prous Science Daily Essentials 1997, June 5.

*Identified compound **257722** Drug Data Report 1998, 020(02): 0155.

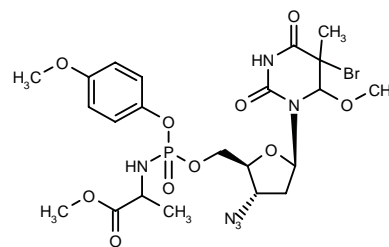
WHI-07**267067**

3'-Azido-5-bromo-5'-*O*-[4-bromophenoxy[1-(methoxycarbonyl)ethylamino]phosphoryl]-3'-deoxy-6-methoxy-5,6-dihydrothymidine



C21 H27 Br2 N6 O9 P; Mol wt: 698.2593

ACTION – Potent anti-HIV and spermicidal agent with IC_{50} (HIV) and EC_{50} (spermicidal activity) values 439- and 13.5-fold lower, respectively, than those of nonoxynol-9. It was shown to produce complete and irreversible loss of sperm motility in a concentration- and time-dependent manner in an *in vitro* assay, without affecting sperm membrane integrity; compound also concentration-dependently reduced (41-100%) the ability of sperm to adhere to and penetrate zona-free hamster ova and bind human zona (99% inhibition). Mice treated intravaginally with WHI-07 before artificial insemination with epididymal sperm showed a marked reduction in fertility (81%), with no damage to the vaginal epithelium or local inflammation. Potentially useful as a vaginal contraceptive for women at high risk for acquiring HIV by heterosexual vaginal transmission. Another aryl phosphate derivative of zidovudine (AZT) with a similar profile of activity is:

**WHI-05 [269950]:** C22 H30 Br N6 O10 P

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

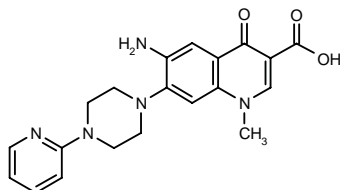
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WM5

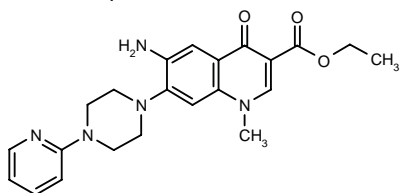
268303

6-Amino-1-methyl-4-oxo-7-[4-(2-pyridinyl)-1-piperazinyl]-1,4-dihydroquinoline-3-carboxylic acid



C20 H21 N5 O3; Mol wt: 379.4179

ACTION – Anti-HIV agent from a series of 6-aminoquinolone compounds, with high activity against HIV-1 and HIV-2 in acutely infected human lymphoblastoid cells ($ED_{50} = 0.01\text{--}0.1\text{ }\mu\text{M}$) and low cytotoxicity ($CC_{50} = 10\text{--}60\text{ }\mu\text{M}$); however, the compound showed poor activity against HIV replication in chronically infected cells. No inhibition of reverse transcriptase or integrase was observed and it only slightly inhibited HIV-1 protease at concentrations of $50\text{ }\mu\text{M}$; further studies suggested that it may interfere with early steps of Tat-driven transcription. Another related compound is:



WM5e [268304]: C22 H25 N5 O3

SOURCES – Università degli Studi di Padova, Padova (IT); Università degli Studi di Perugia, Perugia (IT).

REFERENCES

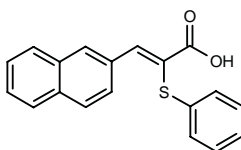
1. Parolin, C. et al. *Anti-HIV activity of a new 6-amino-quinolone compound*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-23.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

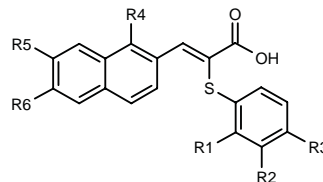
265899

3-(2-Naphthyl)-2-(phenylsulfanyl)-2(*Z*)-propenoic acid



C19 H14 O2 S; Mol wt: 306.3836

ACTION – Cell adhesion inhibitor for the treatment of arthritis, nephritis, asthma, colitis, arteriosclerosis, restenosis, cardiovascular, cerebrovascular and peripheral vascular disorders, tumor growth and metastasis, giving an IC_{50} value of $0.7\text{ }\mu\text{M}$ for inhibition of human neutrophil adhesion. Other representative compounds within this series of naphthalene derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
266700	H	H	H	Br	H	H	C ₁₉ H ₁₃ BrO ₂ S
266701	H	H	H	H	H	OMe	C ₂₀ H ₁₆ O ₃ S
266702	H	H	H	H	H	OH	C ₁₉ H ₁₄ O ₃ S
266703	H	H	H	H	OMe	OMe	C ₂₁ H ₁₈ O ₄ S
266704	H	OMe	H	H	H	H	C ₂₀ H ₁₆ O ₃ S
266705	Cl	H	H	H	H	H	C ₁₉ H ₁₃ ClO ₂ S
266706	H	Cl	H	H	H	H	C ₁₉ H ₁₃ ClO ₂ S
266707	H	H	Cl	H	H	H	C ₁₉ H ₁₃ ClO ₂ S

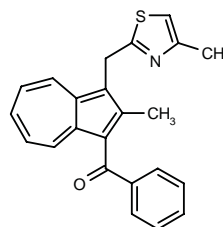
SOURCE – Mitsui Chemicals.

REFERENCES

1. Fukazawa, N. et al. (Mitsui Chemicals, Inc.) *Naphthalene derivs. and medicines containing them as effective ingredient*. JP 98147568.

267524

[2-methyl-3-(4-methyl-1,3-thiazol-2-ylmethyl)-1-azulenyl](phenyl)methanone



C23 H19 N O S; Mol wt: 357.4751

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 0.0012\text{ }\mu\text{M}$ vs. $> 10\text{ }\mu\text{M}$ for COX-1) with excellent antiinflammatory activity in several animal models such as carrageenan-induced edema in rats ($ED_{30} = 5.6\text{ mg/kg p.o.}$; ED_{30} indomethacin = 1.2 mg/kg p.o.) and adjuvant-induced arthritis in rats ($ED_{50} = 3.2\text{ mg/kg p.o.}$; ED_{50} indomethacin = 0.3 mg/kg p.o.), but markedly superior safety compared to indomethacin as regards ulcerogenicity ($UD_{50} > 300\text{ mg/kg p.o.}$ vs. 7.0 mg/kg p.o.).

SOURCE – Kotobuki.

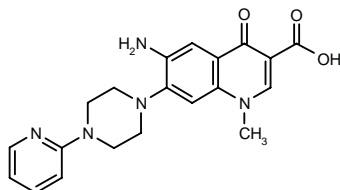
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WM5

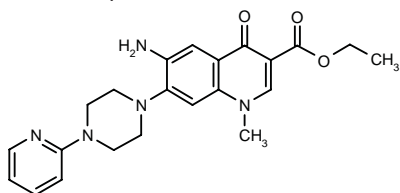
268303

6-Amino-1-methyl-4-oxo-7-[4-(2-pyridinyl)-1-piperazinyl]-1,4-dihydroquinoline-3-carboxylic acid



C20 H21 N5 O3; Mol wt: 379.4179

ACTION – Anti-HIV agent from a series of 6-aminoquinolone compounds, with high activity against HIV-1 and HIV-2 in acutely infected human lymphoblastoid cells ($ED_{50} = 0.01\text{--}0.1\ \mu\text{M}$) and low cytotoxicity ($CC_{50} = 10\text{--}60\ \mu\text{M}$); however, the compound showed poor activity against HIV replication in chronically infected cells. No inhibition of reverse transcriptase or integrase was observed and it only slightly inhibited HIV-1 protease at concentrations of $50\ \mu\text{M}$; further studies suggested that it may interfere with early steps of Tat-driven transcription. Another related compound is:



WM5e [268304]: C22 H25 N5 O3

SOURCES – Università degli Studi di Padova, Padova (IT); Università degli Studi di Perugia, Perugia (IT).

REFERENCES

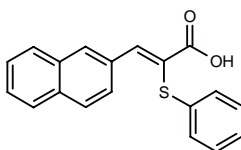
1. Parolin, C. et al. *Anti-HIV activity of a new 6-amino-quinolone compound*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-23.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

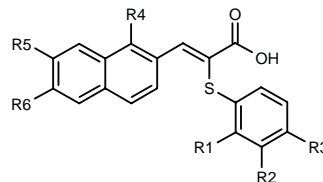
265899

3-(2-Naphthyl)-2-(phenylsulfanyl)-2(*Z*)-propenoic acid



C19 H14 O2 S; Mol wt: 306.3836

ACTION – Cell adhesion inhibitor for the treatment of arthritis, nephritis, asthma, colitis, arteriosclerosis, restenosis, cardiovascular, cerebrovascular and peripheral vascular disorders, tumor growth and metastasis, giving an IC_{50} value of $0.7\ \mu\text{M}$ for inhibition of human neutrophil adhesion. Other representative compounds within this series of naphthalene derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
266700	H	H	H	Br	H	H	C ₁₉ H ₁₃ BrO ₂ S
266701	H	H	H	H	H	OMe	C ₂₀ H ₁₆ O ₃ S
266702	H	H	H	H	H	OH	C ₁₉ H ₁₄ O ₃ S
266703	H	H	H	H	OMe	OMe	C ₂₁ H ₁₈ O ₄ S
266704	H	OMe	H	H	H	H	C ₂₀ H ₁₆ O ₃ S
266705	Cl	H	H	H	H	H	C ₁₉ H ₁₃ ClO ₂ S
266706	H	Cl	H	H	H	H	C ₁₉ H ₁₃ ClO ₂ S
266707	H	H	Cl	H	H	H	C ₁₉ H ₁₃ ClO ₂ S

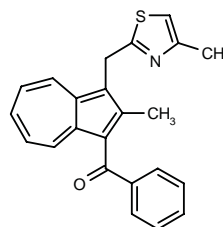
SOURCE – Mitsui Chemicals.

REFERENCES

1. Fukazawa, N. et al. (Mitsui Chemicals, Inc.) *Naphthalene derivs. and medicines containing them as effective ingredient*. JP 98147568.

267524

[2-methyl-3-(4-methyl-1,3-thiazol-2-ylmethyl)-1-azulenyl](phenyl)methanone



C23 H19 N O S; Mol wt: 357.4751

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 0.0012\ \mu\text{M}$ vs. $> 10\ \mu\text{M}$ for COX-1) with excellent antiinflammatory activity in several animal models such as carrageenan-induced edema in rats ($ED_{30} = 5.6\ \text{mg/kg}$ p.o.; ED_{30} indomethacin = $1.2\ \text{mg/kg}$ p.o.) and adjuvant-induced arthritis in rats ($ED_{50} = 3.2\ \text{mg/kg}$ p.o.; ED_{50} indomethacin = $0.3\ \text{mg/kg}$ p.o.), but markedly superior safety compared to indomethacin as regards ulcerogenicity ($UD_{50} > 300\ \text{mg/kg}$ p.o. vs. $7.0\ \text{mg/kg}$ p.o.).

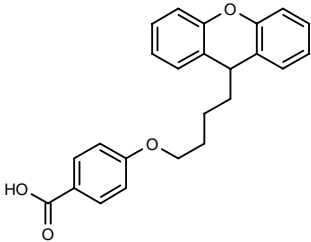
SOURCE – Kotobuki.

REFERENCES

1. Takeuchi, S. et al. *Benzoylazulene derivatives as selective cyclooxygenase-2 inhibitors*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 170.

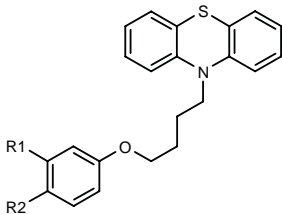
267839

4-[4-(Xanthen-9-yl)butoxy]benzoic acid

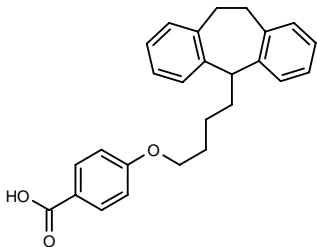


C24 H22 O4; Mol wt: 374.4338

ACTION – Cell adhesion inhibitor proven to inhibit fMLP-stimulated adhesion of human neutrophils *in vitro* (IC₅₀ = 14 μM), potentially useful for the treatment of inflammatory disorders such as rheumatoid arthritis, asthma and colitis, arteriosclerosis, restenosis following PTCA, cardiovascular, cerebrovascular and peripheral vascular disorders, and tumor growth and metastasis. A representative compound from a series of hydroxybenzoic acid derivatives, wherein the following are also included:



Compound	R1	R2	Formula
267840	H	CO2H	C ₂₃ H ₂₁ NO ₃ S
267841	CO2H	H	C ₂₃ H ₂₁ NO ₃ S



267842: C26 H26 O3

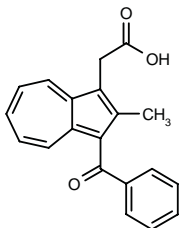
SOURCE – Mitsui Chemicals.

REFERENCES

1. Fukazawa, N. et al. (Mitsui Chemicals, Inc.) *Hydroxy benzoate derivs. and medicines containing them as effective ingredient*. JP 98182550.

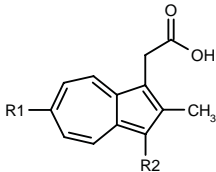
267843^{1,2}

2-(3-Benzoyl-2-methylazulen-1-yl)acetic acid



C20 H16 O3; Mol wt: 304.3434

ACTION – Antiinflammatory, antiarthritic and analgesic agent, an inhibitor of cyclooxygenase (COX) with selectivity for COX-2 (IC₅₀ = 0.13 μM) relative to COX-1 (IC₅₀ = 3.1 μM). Antiinflammatory activity was assessed *in vivo* in the carrageenan-induced rat paw edema model (40% inhibition at 2.8 mg/kg p.o.). Within this series of azulene derivatives, the following are also included:



Compound	R1	R2	Formula
267844 ¹	i-Pr	COPh	C ₂₃ H ₂₂ O ₃
267845 ¹	H	2-Cl-PhCO	C ₂₀ H ₁₅ ClO ₃
267846 ^{1,2}	H	4-Cl-PhCO	C ₂₀ H ₁₅ ClO ₃
267847 ^{1,2}	H	4-Br-PhCO	C ₂₀ H ₁₅ BrO ₃
267848 ¹	i-Pr	4-Br-PhCO	C ₂₃ H ₂₁ BrO ₃
267849 ^{1,2}	H	4-Me-PhCO	C ₂₁ H ₁₈ O ₃
267850 ^{1,2}	H	4-MeO-PhCO	C ₂₁ H ₁₈ O ₄
267851 ¹	H	2-thienyl-CO	C ₁₈ H ₁₄ O ₃ S
267852 ¹	H	4-Cl-PhCH2	C ₂₀ H ₁₇ ClO ₂

SOURCE – Kotobuki.

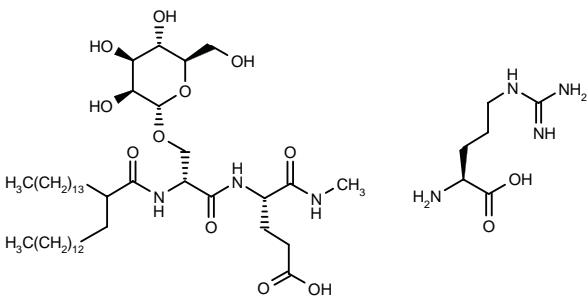
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1. Toyama, T. et al. (Kotobuki Pharmaceutical Co., Ltd.) *Azulene derivs., their preparation method and agents containing them*. JP 98182546.

2. Takeuchi, S. et al. *Benzoylazulene derivatives as selective cyclooxygenase-2 inhibitors*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 170.

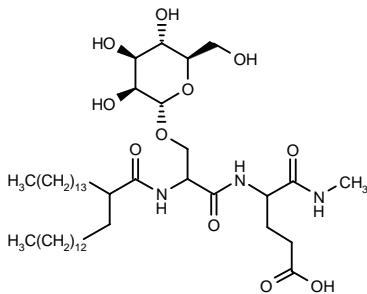
268023

N-(2-Tetradecylhexadecanoyl)-O³-(α-D-mannopyranosyl)-D-seryl-L-glutamic acid 1-methylamide L-arginine salt



C45 H85 N3 O11 . C6 H14 N4 O2; Mol wt: 1018.3790

ACTION – Antiarthritic and antiinflammatory agent, an inhibitor of E-selectin (IC₅₀ = 3.3 μM), P-selectin (IC₅₀ = 0.7 μM) and L-selectin (IC₅₀ = 2.6 μM) binding. Other representative compounds within this series of mannopyranosyl derivatives include the following:



Compound	Isomer	Formula
268024	L,L	C ₄₅ H ₈₅ N ₃ O ₁₁
268025	L,D	C ₄₅ H ₈₅ N ₃ O ₁₁
268026	D,L	C ₄₅ H ₈₅ N ₃ O ₁₁
268027	D,D	C ₄₅ H ₈₅ N ₃ O ₁₁

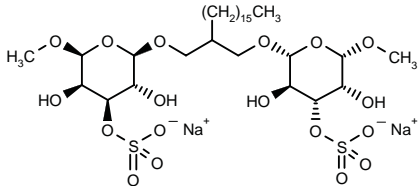
SOURCE – Kanebo.

REFERENCES

1. Achiwa, H. et al. (Kanebo, Ltd.) *Mannopyranosyl derivs., agents containing them as effective ingredient and intermediates for their production.* JP 98204096.

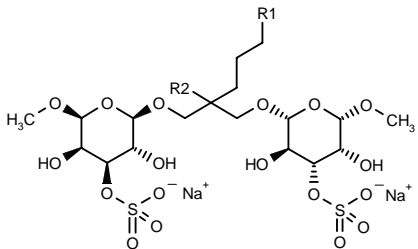
268063

2-Hexadecyl-1,3-bis-*O*-(3-*O*-sulfo-β-D-galactopyranosyl)-1,3-propanediol disodium salt



C31 H58 Na2 O18 S2; Mol wt: 828.8932

ACTION – Antiinflammatory agent that acts by virtue of its ability to inhibit ligand binding to selectins. Within this series of sulfated and phosphorylated galactose derivatives, the following are also included:



Compound	R1	R2	Formula
268064	C11H23	H	C ₂₉ H ₅₄ Na ₂ O ₁₈ S ₂
268065	C7H15	H	C ₂₅ H ₄₆ Na ₂ O ₁₈ S ₂
268066	C19H39	H	C ₃₇ H ₇₀ Na ₂ O ₁₈ S ₂
268067	H	Pr	C ₂₁ H ₃₈ Na ₂ O ₁₈ S ₂

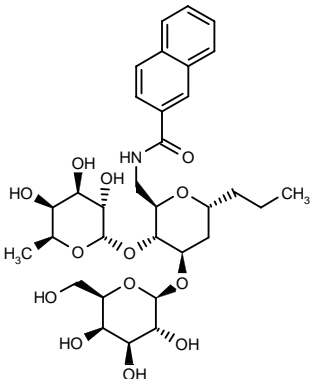
SOURCE – Sanwa.

REFERENCES

1. Igami, T. et al. (Sanwa Kagaku Kenkyusho Co., Ltd.) *Novel sulfated and phosphorylated galactose derivs. and their method.* JP 98195094.

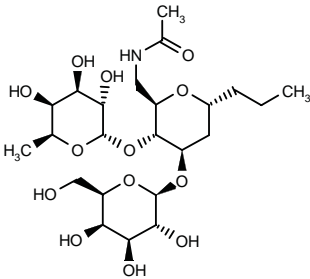
268068

1,2,6-Trideoxy-4-*O*-(α-L-galactopyranosyl)-3-*O*-(β-D-galactopyranosyl)-6-(2-naphthylcarboxamido)-1-propyl-α-D-glucopyranose



C32 H45 N O13; Mol wt: 651.7015

ACTION – Agent for the treatment of inflammation, asthma, cancer, autoimmune diseases and ischemia–reperfusion disorders, an inhibitor of cell adhesion proven to inhibit P-selectin-mediated adhesion of HL-60 cells to human platelets (56% inhibition at 6.6 mM). Another compound from this series of C-glycoside derivatives is:



269190: C23 H41 N O13

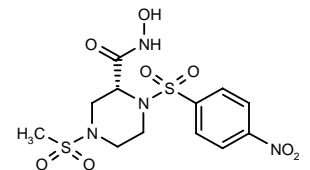
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Imazaki, N. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *C-Glycoside derivs.* JP 98195097.

268246

4-(Methylsulfonyl)-1-(4-nitrophenylsulfonyl)piperazine-2(*R*)-carbohydroxamic acid



C12 H16 N4 O8 S2; Mol wt: 408.4104

ACTION – Inhibitor of tumor necrosis factor (TNF) production and matrix metalloproteinases (MMPs) such as collagenase (95.3% inhibition at 1 μM using human enzyme from IL-1β-stimulated human skin fibroblasts). Claimed for use in the treatment of MMP- or TNF-α-mediated disorders such as arthritis, cancer, periodontal disease, psoriasis, AIDS and septic shock. A representative compound within a series of piperazine derivatives.

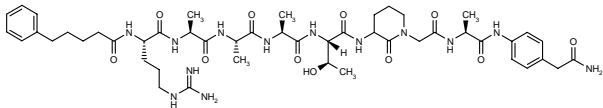
SOURCE – Fujisawa.

REFERENCES

1. Neya, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Piperazine cpds. as inhibitors of MMP or TNF*. WO 9827069.

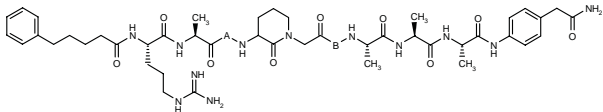
268256

2-[4-[N-[2-[2-Oxo-3-(5-phenylpentanoyl-arginyl-alanyl-alanyl-alanyl-threonylamino)piperidin-1-yl]acetyl]-alanylaminophenyl]acetamide



C48 H71 N13 O11; Mol wt: 1006.1690

ACTION – Antiarthritic agent, an inhibitor of peptide binding to major histocompatibility complex (MHC) class II proteins capable of preventing a T-cell immune response mediated by or through an MHC class II molecule. It showed significant binding to HLA-DR4Dw4 at a concentration of 0.1 μM or less, and *in vivo* activity was demonstrated by inhibition of delayed-type hypersensitivity in mice at a dose of about 1 mg/kg/day by osmotic minipump. Other specifically claimed peptides include the following:



Compound	A	B	Formula
268257	-L-Ala-	bond	C ₄₇ H ₆₉ N ₁₃ O ₁₀
268258	bond	-L-Thr-	C ₄₈ H ₇₁ N ₁₃ O ₁₁

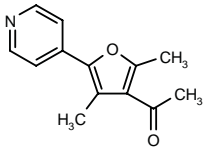
SOURCE – Zeneca.

REFERENCES

1. Luke, R.W.A. and Cotton, R. (Zeneca Ltd.) *Inhibitors of peptide binding to MHC class II proteins*. WO 9825951.

268367

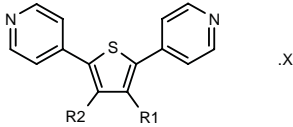
1-[2,4-Dimethyl-5-(4-pyridyl)furan-3-yl]ethanone



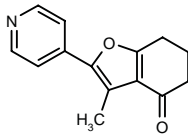
C13 H13 N O2; Mol wt: 215.2507

ACTION – An inhibitor of the production of cytokines such as tumor necrosis factor (TNF-α) and IL-1 and/or the expression of cell adhesion molecules (CAMs), with potential in the treatment of a broad range of disorders including arthritis, asthma, inflammatory bowel disease, sepsis, rhinitis, AIDS, osteoporosis, cardiovascular

disorders, cachexia, psoriasis, thrombosis, diabetes, transplant rejection, graft-versus-host disease, gout and cancer. Other specifically claimed compounds from this series of pyridylfuran and pyridylthiophene derivatives include the following:



Compound	R1	R2	X	Formula
268369	Me	Ac		C ₁₇ H ₁₄ N ₂ OS
268370	-CH2CH2CO-			C ₁₇ H ₁₂ N ₂ OS
268371	Me	Et	2HCl	C ₁₇ H ₁₆ N ₂ S.2HCl
268372	Me	CH=NOH	2HCl	C ₁₆ H ₁₃ N ₃ OS.2HCl
268373	Me	CH=NOAc		C ₁₈ H ₁₅ N ₃ O ₂ S



268368: C14 H13 N O2

SOURCE – Pfizer.

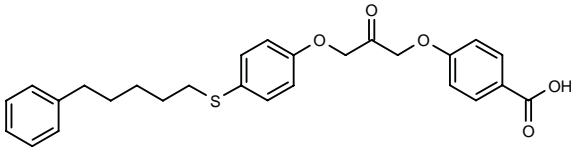
REFERENCES

1. Kawai, A. and Kawai, M. (Pfizer Inc.) *Pyridylfuran and pyridylthiophene cpds. and pharmaceutical use thereof*. EP 853083.

AR-C73346XX

267574

4-[2-Oxo-3-[4-(5-phenylpentylsulfanyl)phenoxy]propoxy]benzoic acid



C27 H28 O5 S; Mol wt: 464.5792

ACTION – Potential antiinflammatory agent, a potent inhibitor of cytosolic phospholipase A₂ (cPLA₂; IC₅₀ = 0.08 μM; IC₅₀ in HL60 cells = 1.5 μM) that appears to form a reversible 1:1 complex with the enzyme.

SOURCE – Astra Charnwood.

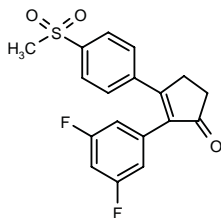
REFERENCES

1. Mete, A. et al. *1,3-Disubstituted propan-2-ones: A novel series of potent inhibitors of cytosolic phospholipase A₂ (cPLA₂)*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.250.

L-776967

267585

2-(3,5-Difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one



C18 H14 F2 O3 S; Mol wt: 348.3676

ACTION – Potent and selective inhibitor of cyclooxygenase type 2 (COX-2).

SOURCE – Merck & Co.

REFERENCES

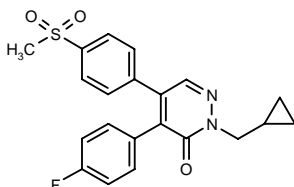
1. Black, C. (Merck Frosst Canada Inc.) 2-(3,5-Difluorophenyl)-3-(4-(methyl-sulfonyl)-phenyl)-2-cyclopenten-1-one useful as an inhibitor of cyclooxygenase-2. EP 863134, JP 98251220.

2. Zhao, D. et al. Convergent syntheses of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl-phenyl)cyclopent-2-enone, L-776,967, a potent COX-2 inhibitor. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 158.

L-818571

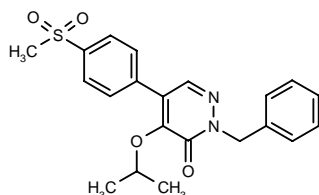
267564

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyridazin-3(2H)-one



C21 H19 F N2 O3 S; Mol wt: 398.4561

ACTION – Antiinflammatory agent, a potent and selective cyclooxygenase type 2 (COX-2) inhibitor reported to have good activity *in vivo*. Another compound from this series of pyridazinones is:



L-804600 [267565]: C21 H22 N2 O4 S

SOURCE – Merck Frosst.

REFERENCES

1. Li, C.S. et al. (Merck Frosst Canada Inc.) Pyridazinones as inhibitors of cyclooxygenase-2. WO 9841511.

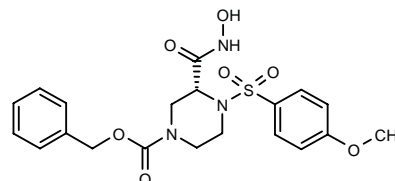
2. Li, C.-S. et al. Pyridazinones as selective cyclooxygenase-2 inhibitors. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 032.

PGE-2946979

267515

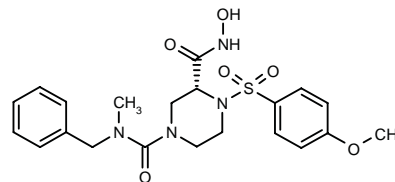
263347 (undefined isomer)*

4-(Benzyloxycarbonyl)-1-(4-methoxyphenylsulfonyl)-piperazine-2(R)-carbohydroxamic acid



C20 H23 N3 O7 S; Mol wt: 449.4817

ACTION – Antiarthritic agent, a potent, broad-spectrum matrix metalloproteinase (MMP) inhibitor with IC₅₀ values of 24, 0.8, 18, 232, 2 and 1 nM, respectively, against collagenase 1 (MMP-1), gelatinase A (MMP-2), stromelysin (MMP-3), matrilysin (MMP-7), gelatinase B (MMP-9) and collagenase 3 (MMP-13), reported to have oral activity in a rat arthritis model. Another piperazine-based MMP inhibitor is:



PGE-5747401 [267516]: C21 H26 N4 O6 S

SOURCE – Procter & Gamble.

REFERENCES

1. De, B. et al. (The Procter & Gamble Co.) 1,4-Heterocyclic metalloprotease inhibitors. WO 9808825.

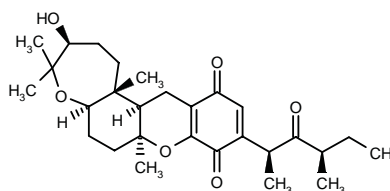
2. Cheng, M. et al. Design and synthesis of piperazine-based MMP inhibitors. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 044.

*Drug Data Report 1998, 020(06): 0531.

TAN-2474A

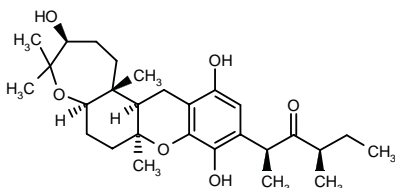
267902

[3S-(3 α ,5 α ,7 α ,13 α ,13 β)]-10-[1(S),3(R)-Dimethyl-2-oxopentyl]-3-hydroxy-4,4,7 α ,13 β -tetramethyl-2,3,4,5 α ,6,7,7 α ,9,12,13,13 α ,13 β -dodecahydro-1H-oxepino[3,2-a]xanthene-9,12-dione



C28 H40 O6; Mol wt: 472.6180

ACTION – Complement C5a antagonist isolated from *Gliocladium* sp. FL-66930 (FERM BP-5717), giving an IC_{50} value of 2 μ g/ml in a binding assay using [125 I]-C5a as the radioligand in myeloid P39 (+) cells. Potentially useful for the treatment of a broad range of disorders including inflammation, septicemia, adult respiratory distress syndrome, asthma, atherosclerotic aneurysm, myocardial ischemia, cerebral infarction, pneumonia, nephritis, hepatitis, pancreatitis and psoriasis. Another compound isolated from the same source is:



TAN-2474B [267903]: C28 H42 O6

SOURCE – Takeda.

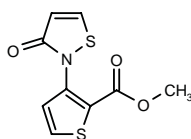
REFERENCES

1. Tsuboya, S. et al. (Takeda Chemical Industries, Ltd.) *TAN-2474 related cpds., their preparation method and their use.* JP 98182648.

IMMUNOMODULATING AGENTS

267523

3-(3-Oxo-2,3-dihydroisothiazol-2-yl)thiophene-2-carboxylic acid methyl ester



C9 H7 N O3 S2; Mol wt: 241.2903

ACTION – Potent and selective T-cell p56^{lck} tyrosine kinase inhibitor (IC_{50} = 7 μ M) potentially useful as an immunosuppressant for use in the treatment of auto-immune diseases and transplant rejection.

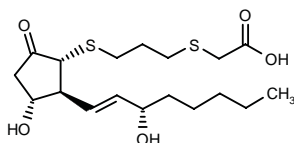
SOURCE – Abbott.

REFERENCES

1. Tu, N.P. et al. *Inhibition of p56^{lck} tyrosine kinase by methyl 3-(N-isothiazolone)-2-thiophenecarboxylate: Structure activity relationship and mechanism of action studies.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 261.

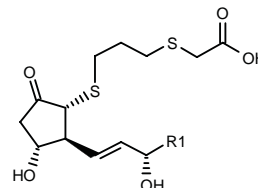
268355

11 α ,15 α -Dihydroxy-9-oxo-3,7-dithia-13(E)-prostenoic acid



C18 H30 O5 S2; Mol wt: 390.5620

ACTION – Agent for the treatment of immunological diseases, asthma, abnormal bone formation, neuronal cell death, nephritis and hypertension that displays strong binding affinity for the PGE₂ EP₄ receptor subtype (K_i = 0.0007 μ M against [3 H]-PGE₂ binding to murine receptor expressed in CHO cells) but much less affinity for the EP_{3 α} receptor subtype (K_i = 1.5 μ M). Within this series of specifically claimed 3,7-dithiaprostanic acid derivatives, the following are also included:



Compound	R1	Formula
268356	cyclohexyl	C ₁₉ H ₃₀ O ₅ S ₂
268357	CH2Ph	C ₂₀ H ₂₆ O ₅ S ₂
268358	cyclohexyl-CH2	C ₂₀ H ₃₂ O ₅ S ₂

SOURCE – Ono.

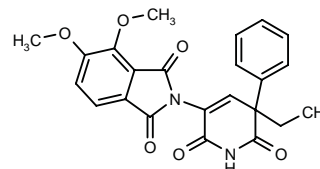
REFERENCES

1. Maruyama, T. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *A 3,7-dithiaprostanic acid deriv.* EP 855389, JP 98265454.

268649

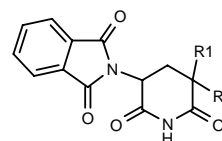
2-(5-Ethyl-2,6-dioxo-5-phenyl-1,2,5,6-tetrahydropyridin-3-yl)-4,5-dimethoxy-2,3-dihydro-1H-isindole-1,3-dione

N-(5-Ethyl-2,6-dioxo-5-phenyl-1,2,5,6-tetrahydropyridin-3-yl)-3,4-dimethoxyphthalimide



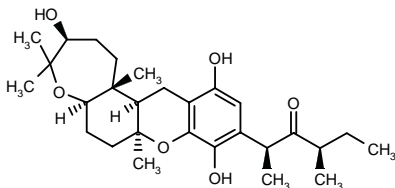
C23 H20 N2 O6; Mol wt: 420.4190

ACTION – Immunomodulating agent proven to inhibit the lipopolysaccharide (LPS)-induced release of tumor necrosis factor- α (TNF- α ; IC_{50} = 2.0 μ g/ml), as well as the CD2/CD28- or TSST-1-induced release of IL-2 (86 ± 6 and $77 \pm 20\%$ inhibition, respectively, at 50 μ g/ml) from human peripheral blood mononuclear cells. Other exemplified compounds from this series of thalidomide analogs include the following:



Compound	R1	R2	Formula
268650	H	Me	C ₁₄ H ₁₂ N ₂ O ₄
268651	H	Ph	C ₁₉ H ₁₄ N ₂ O ₄
268652	Et	Ph	C ₂₁ H ₁₈ N ₂ O ₄

ACTION – Complement C5a antagonist isolated from *Gliocladium* sp. FL-66930 (FERM BP-5717), giving an IC₅₀ value of 2 µg/ml in a binding assay using [¹²⁵I]-C5a as the radioligand in myeloid P39 (+) cells. Potentially useful for the treatment of a broad range of disorders including inflammation, septicemia, adult respiratory distress syndrome, asthma, atherosclerotic aneurysm, myocardial ischemia, cerebral infarction, pneumonia, nephritis, hepatitis, pancreatitis and psoriasis. Another compound isolated from the same source is:



TAN-2474B [267903]: C28 H42 O6

SOURCE – Takeda.

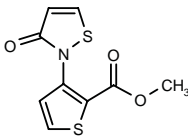
REFERENCES

1. Tsuboya, S. et al. (Takeda Chemical Industries, Ltd.) *TAN-2474 related cpds., their preparation method and their use.* JP 98182648.

IMMUNOMODULATING AGENTS

267523

3-(3-Oxo-2,3-dihydroisothiazol-2-yl)thiophene-2-carboxylic acid methyl ester



C9 H7 N O3 S2; Mol wt: 241.2903

ACTION – Potent and selective T-cell p56^{lck} tyrosine kinase inhibitor (IC₅₀ = 7 µM) potentially useful as an immunosuppressant for use in the treatment of auto-immune diseases and transplant rejection.

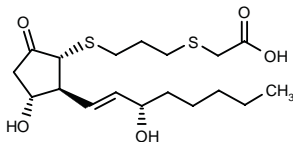
SOURCE – Abbott.

REFERENCES

1. Tu, N.P. et al. *Inhibition of p56^{lck} tyrosine kinase by methyl 3-(N-isothiazolone)-2-thiophenecarboxylate: Structure activity relationship and mechanism of action studies.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 261.

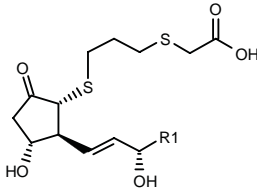
268355

11α,15α-Dihydroxy-9-oxo-3,7-dithia-13(E)-prostenoic acid



C18 H30 O5 S2; Mol wt: 390.5620

ACTION – Agent for the treatment of immunological diseases, asthma, abnormal bone formation, neuronal cell death, nephritis and hypertension that displays strong binding affinity for the PGE₂ EP₄ receptor subtype (K_i = 0.0007 µM against [³H]-PGE₂ binding to murine receptor expressed in CHO cells) but much less affinity for the EP_{3α} receptor subtype (K_i = 1.5 µM). Within this series of specifically claimed 3,7-dithiaprostanic acid derivatives, the following are also included:



Compound	R1	Formula
268356	cyclohexyl	C ₁₉ H ₃₀ O ₅ S ₂
268357	CH2Ph	C ₂₀ H ₂₆ O ₅ S ₂
268358	cyclohexyl-CH2	C ₂₀ H ₃₂ O ₅ S ₂

SOURCE – Ono.

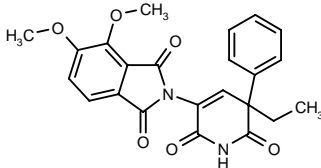
REFERENCES

1. Maruyama, T. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *A 3,7-dithiaprostanic acid deriv.* EP 855389, JP 98265454.

268649

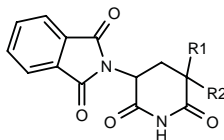
2-(5-Ethyl-2,6-dioxo-5-phenyl-1,2,5,6-tetrahydropyridin-3-yl)-4,5-dimethoxy-2,3-dihydro-1H-isindole-1,3-dione

N-(5-Ethyl-2,6-dioxo-5-phenyl-1,2,5,6-tetrahydropyridin-3-yl)-3,4-dimethoxyphthalimide



C23 H20 N2 O6; Mol wt: 420.4190

ACTION – Immunomodulating agent proven to inhibit the lipopolysaccharide (LPS)-induced release of tumor necrosis factor-α (TNF-α; IC₅₀ = 2.0 µg/ml), as well as the CD2/CD28- or TSST-1-induced release of IL-2 (86 ± 6 and 77 ± 20% inhibition, respectively, at 50 µg/ml) from human peripheral blood mononuclear cells. Other exemplified compounds from this series of thalidomide analogs include the following:



Compound	R1	R2	Formula
268650	H	Me	C ₁₄ H ₁₂ N ₂ O ₄
268651	H	Ph	C ₁₉ H ₁₄ N ₂ O ₄
268652	Et	Ph	C ₂₁ H ₁₈ N ₂ O ₄

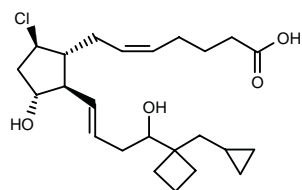
SOURCE – Grünenthal.

REFERENCES

1. Zimmer, O. et al. (Grünenthal GmbH) *Thalidomide analogues from the piperidine-2,6-dione class*. EP 856513, JP 98316675.

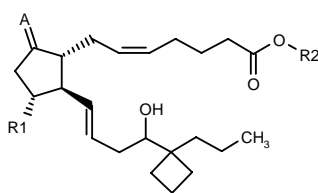
268670

(5*Z*,9β,11α,13*E*)-9-Chloro-11,16-dihydroxy-19,20-methano-17,17-propanoprost-5,13-dienoic acid



C24 H37 Cl O4; Mol wt: 425.0053

ACTION – Prostaglandin E₂ (PGE₂) derivative with potent and selective affinity for EP₂ receptors relative to other PGE₂ receptor subtypes, as shown in a binding assay by K_i values of 0.0009, 1.10, 2.70 and 0.40 μM, respectively, for murine EP₂, EP₁, EP_{3α} and EP₄ receptors expressed in CHO cells. Potentially useful for the treatment or prevention of immunological disorders, asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retinal neuropathy of glaucoma. Within this series of specifically claimed ω-cycloalkyl-prostaglandin E₂ derivatives, the following are also included:



Compound	R1	R2	A	Formula
268671	H	H	O	C ₂₃ H ₃₆ O ₄
268672	OMe	Me	O	C ₂₅ H ₄₀ O ₅
268673	OH	Me	CH2	C ₂₅ H ₄₀ O ₄

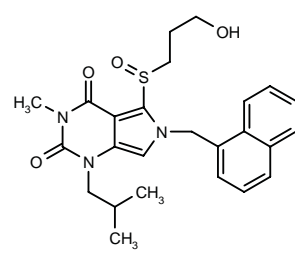
SOURCE – Ono.

REFERENCES

1. Tani, K. and Ohuchida, S. (Ono Pharmaceutical Co., Ltd.) *Omega-cycloalkyl-prostaglandin E₂ derivs.* EP 860430.

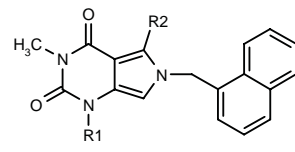
268946

5-(3-Hydroxypropylsulfinyl)-1-isobutyl-3-methyl-6-(1-naphthylmethyl)-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*d*]pyrimidine-2,4-dione



C25 H29 N3 O4 S; Mol wt: 467.5871

ACTION – Immunosuppressive agent proven to inhibit human lymphocyte proliferation in the mixed lymphocyte reaction (MRL) test with an IC₅₀ value of < 1 μM. Potentially useful for the treatment of transplant rejection, autoimmune, inflammatory, proliferative and hyperproliferative diseases, as well as reversible obstructive airways disease. A representative compound from a series of pyrrolo[3,4-*d*]pyrimidinone derivatives, wherein the following are also included:



Compound	R1	R2	Formula
268947	i-Bu	SO2(CH2)3OH	C ₂₅ H ₂₉ N ₃ O ₅ S
268948	i-Bu	SCH2CH2CO2H	C ₂₅ H ₂₇ N ₃ O ₄ S
268949	i-Pr	SO(CH2)3OH	C ₂₄ H ₂₇ N ₃ O ₄ S
268950	i-Bu	ethynylene-CH2CH2OH	C ₂₆ H ₂₇ N ₃ O ₃
268951	i-Bu	2-Pyr-S	C ₂₇ H ₂₆ N ₄ O ₂ S
268952	i-Bu	4-MeO-PhS	C ₂₉ H ₂₉ N ₃ O ₃ S

SOURCE – Astra.

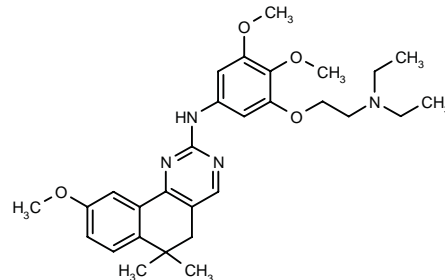
REFERENCES

1. Cooper, M. et al. (Astra Pharmaceuticals Ltd.,Astra AB) *Pyrrolo[3,4-*d*]pyrimidinone derivs. and their use as medicaments*. WO 9828301.

CT-5269

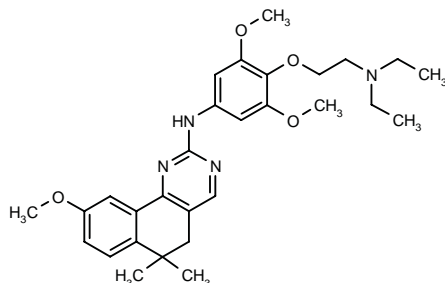
267577

N-[3-[2-(Diethylamino)ethoxy]-4,5-dimethoxyphenyl]-9-methoxy-6,6-dimethyl-5,6-dihydrobenzo[*h*]quinazolin-2-amine

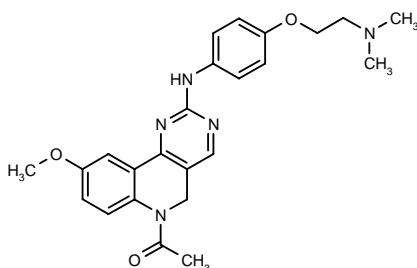


C29 H38 N4 O4; Mol wt: 506.6432

ACTION – Potential immunomodulating agent for use in autoimmune diseases and transplant rejection, a potent and selective inhibitor of p56^{lck} protein tyrosine kinase (IC₅₀ = 1.1 nM vs. > 10,000, 3155, 86 and 8462 nM, respectively, for protein kinase C [PKC], epidermal growth factor [EGF] receptor, csk and cdc2 kinases); it also inhibits other members of the src family (IC₅₀ = 6.4, 27, 13 and 4.1 nM, respectively, against src, fyn, lyn and yes). Other related compounds are:



CT-5276 [267582]: C29 H38 N4 O4



CT-5652 [267583]: C24 H27 N5 O3

SOURCE – Celltech.

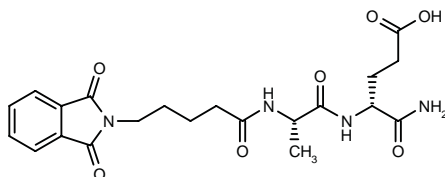
REFERENCES

1. Davis, J.M. et al. (Celltech Therapeutics Ltd.) *Fused polycyclic 2-aminopyrimidine derivs., their preparation and their use as protein tyrosine kinase inhibitors*. WO 9828281.
2. Davis, J.M. et al. *Benzo[h]-5,6-dihydroquinazoline-2-amines as potent and selective inhibitors of p56^{lck}*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.234.

LK-413

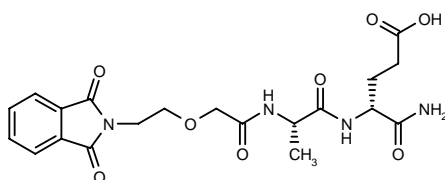
267809

5-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)pentanoyl-L-alanyl-D-glutamic acid 1-amide



C21 H26 N4 O7; Mol wt: 446.4574

ACTION – Immunomodulating agent selected for further evaluation from a series of phthalimido desmuramyl dipeptides along with the following compound:



LK-423 [267810]: C20 H24 N4 O8

SOURCES – LEK; University of Ljubljana, Ljubljana (SI).

REFERENCES

1. Pecar, S. et al. (University of Ljubljana; LEK Pharmaceutical and Chemical Co.) *Novel N-acyldipeptides, processes for the preparation thereof and pharmaceutical compsns. containing the same*. EP 477912, JP 94220087.
2. Sollner, M. et al. *Immunomodulatory properties of phthalimido desmuramyl dipeptides*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.325.
3. Urleb, U. et al. *Synthesis of phthalimido-desmuramylpeptide analogues as potential immunomodulating agents*. Arch Pharm 1995, 328(2): 113.

PncCRM9

268310

9-Valent (types 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal vaccine conjugated to CRM₁₉₇

ACTION – Multivalent conjugate pneumococcal vaccine proven to be well tolerated and highly immunogenic in small children. The vaccine induces immunologic memory and functionally active antibodies. Reduction in nasopharyngeal carriage rate of the pneumococcal serotypes included in the vaccine was observed, whereas the carriage rate of other serotypes remained constant or increased. Large-scale efficacy trials are in progress in invasive infections, pneumonia and otitis media.

SOURCE – Wyeth-Ayerst.

REFERENCES

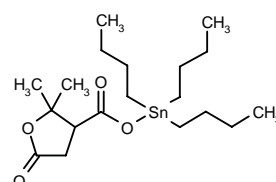
1. Dagan, R. et al. *Tolerability and immunogenicity of a 9-valent pneumococcal CRM₁₉₇ vaccine (PncCRM9) vs. meningococcal group C CRM₁₉₇ vaccine (MncCRM-C) during 2nd and 3rd year of life: A double-blind randomized study*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst G-51.
2. Dagan, R. et al. *Effect of a 9-valent pneumococcal vaccine conjugates to CRM₁₉₇ (PncCRM9) on nasopharyngeal (NP) carriage of vaccine type and non-vaccine type S. pneumoniae (Pnc) strains among day care center (DC) attendees*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst G-52.
3. Eskola, J. et al. *Pneumococcal conjugate vaccines: Immunogenicity, effects on colonization, and prospects for clinical efficacy*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst S-45.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

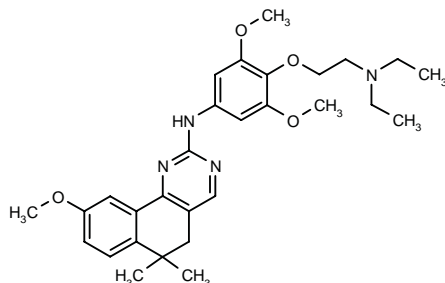
265436

2,2-Dimethyl-5-oxotetrahydrofuran-3-carboxylic acid tributyltin ester

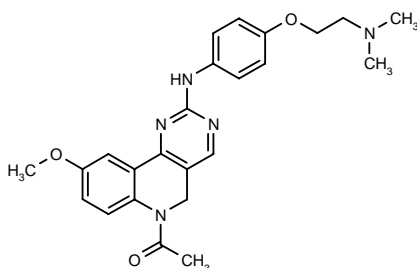


C19 H36 O4 Sn; Mol wt: 447.1994

ACTION – Potential immunomodulating agent for use in autoimmune diseases and transplant rejection, a potent and selective inhibitor of p56^{lck} protein tyrosine kinase (IC_{50} = 1.1 nM vs. > 10,000, 3155, 86 and 8462 nM, respectively, for protein kinase C [PKC], epidermal growth factor [EGF] receptor, csk and cdc2 kinases); it also inhibits other members of the src family (IC_{50} = 6.4, 27, 13 and 4.1 nM, respectively, against src, fyn, lyn and yes). Other related compounds are:



CT-5276 [267582]: C29 H38 N4 O4



CT-5652 [267583]: C24 H27 N5 O3

SOURCE – Celltech.

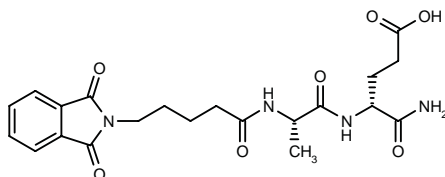
REFERENCES

1. Davis, J.M. et al. (Celltech Therapeutics Ltd.) *Fused polycyclic 2-aminopyrimidine derivs., their preparation and their use as protein tyrosine kinase inhibitors*. WO 9828281.
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LK-413

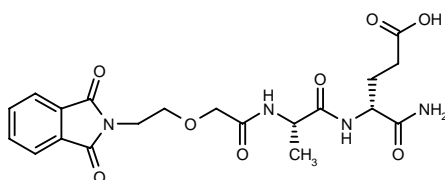
267809

5-(1,3-Dioxo-1,3-dihydro-2H-isindol-2-yl)pentanoyl-L-alanyl-D-glutamic acid 1-amide



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SOURCES – LEK; University of Ljubljana, Ljubljana (SI).

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3. Urleb, U. et al. *Synthesis of phthalimido-desmuramylpeptide analogues as potential immunomodulating agents*. Arch Pharm 1995, 328(2): 113.

PncCRM9

268310

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SOURCE – Wyeth-Ayerst.

REFERENCES

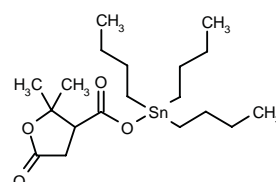
1. Dagan, R. et al. *Tolerability and immunogenicity of a 9-valent pneumococcal CRM₁₉₇ vaccine (PncCRM9) vs. meningococcal group C CRM₁₉₇ vaccine (MncCRM-C) during 2nd and 3rd year of life: A double-blind randomized study*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst G-51.
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3. Eskola, J. et al. *Pneumococcal conjugate vaccines: Immunogenicity, effects on colonization, and prospects for clinical efficacy*. 39th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst S-45.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

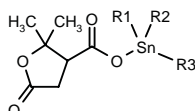
265436

2,2-Dimethyl-5-oxotetrahydrofuran-3-carboxylic acid tributyltin ester



C19 H36 O4 Sn; Mol wt: 447.1994

ACTION – Antineoplastic agent with markedly superior *in vitro* activity compared to carboplatin and cisplatin against various tumor cell lines including human breast cancer MCF-7 (ID₅₀ = 3, 10,500 and 1400 ng/ml, respectively), ovarian cancer IGROV (ID₅₀ = 4, 2400 and 230 ng/ml, respectively), colon cancer WiDr (ID₅₀ = 11, 3500 and 1550 ng/ml, respectively), melanoma M19MEL (ID₅₀ = 11, 5500 and 780 ng/ml, respectively), renal cancer A498 (ID₅₀ = 15, 18,000 and 1200 ng/ml, respectively) and non-small cell lung cancer H226 cells (ID₅₀ = 8, 25,000 and 3158 ng/ml, respectively). Other exemplified organotin compounds include the following:



Compound	R1	R2	R3	Formula
266689	Bu	2,2-(Me)2-5-oxo-3-THF-COO	Bu	C ₂₂ H ₃₆ O ₈ Sn
266690	Ph	Ph	Ph	C ₂₅ H ₂₄ O ₄ Sn

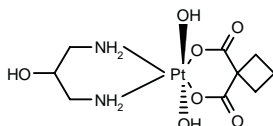
SOURCE – Pharmachemie.

REFERENCES

1. Gielen, M. et al. (Pharmachemie BV) *Organotin cpds. and compsns. containing these cpds.* EP 848008, JP 98182672.

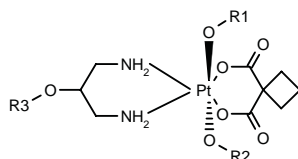
268605

(OC-6-33)-(1,1-Cyclobutanedicarboxylato)(dihydroxo)(2-hydroxypropane-1,3-diamine)platinum



C9 H18 N2 O7 Pt; Mol wt: 461.3282

ACTION – Orally active platinum complex that exhibited potent antitumor properties in mice bearing murine reticulosarcoma M5076 (ID₅₀ < 8.0 mg/kg/day p.o. x 5 days) and low toxicity (LD₅₀ > 200.0 mg/kg i.p.); maximum growth inhibition was 95.6% at 32.0 mg/kg. Other related compounds include the following:



Compound	R1=R2	R3	Formula
268606	Ac	H	C ₁₃ H ₂₂ N ₂ O ₉ Pt
268607	COCF3	COCF3	C ₁₅ H ₁₅ F ₆ N ₂ O ₁₀ Pt
268608	COCF3	H	C ₁₃ H ₁₆ F ₆ N ₂ O ₉ Pt

SOURCE – SS Pharmaceutical.

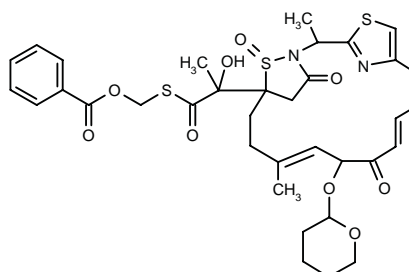
REFERENCES

1. Mogi, K. et al. (SS Pharmaceutical, Ltd.) *Platinum(IV) complex and pharmaceutical compsn. comprising the same.* EP 864578, JP 98251285.

ANTIBIOTICS AND ALKALOIDS

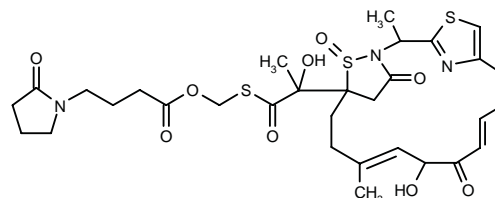
267956

17-[2-(Benzoyloxymethylsulfanyl)-1-hydroxy-1-methyl-2-oxoethyl]-2,14-dimethyl-12-(2-tetrahydropyranyloxy)-4,20-dithia-1,21-diazatricyclo[15.2.1.1^{3,6}]heneicos-3(21),5,7,9,13-pentaene-11,19-dione 20-oxide



C35 H40 N2 O9 S3; Mol wt: 728.9040

ACTION – Antineoplastic and antibacterial agent with potent *in vitro* cytotoxicity against HeLa S3 cells (IC₅₀ = 0.050 μM). Antitumor activity was demonstrated *in vivo* in mice bearing murine S180 solid tumors (T/C = 0.23 at 4.0 mg/kg i.v.). Another compound from this series of DC-107 derivatives is:



267957: C31 H39 N3 O9 S3

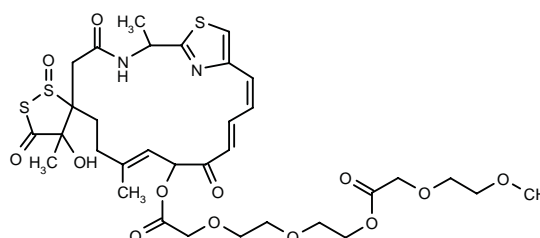
SOURCE – Kyowa Hakko.

REFERENCES

1. Arai, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *DC 107 derivs. (1).* WO 9825933.

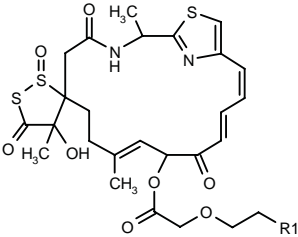
267958

4-Hydroxy-2',4,9'-trimethyl-11'-(10-oxo-3,6,9,12,15-pentaoxahexadecanoyloxy)spiro[1,2-dithiolane-3,6'-[19]thia[3,20]diazabicyclo[15.2.1]eicos-1(20),9,13,15,17-pentaene]-4',5,12'-trione S²-oxide

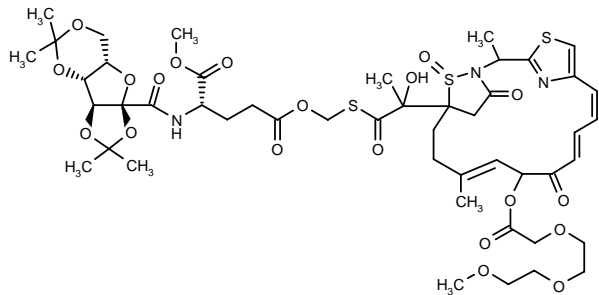


C33 H44 N2 O13 S3; Mol wt: 772.9096

ACTION – Antineoplastic and antibacterial agent proven to potently inhibit the growth of sarcoma 180 tumors implanted s.c. in mice, giving a T/C value of 0.12 at 8.0 mg/kg i.v. Antibacterial activity was tested *in vitro* against *Enterococcus hirae* ATCC 10541, *Staphylococcus aureus* ATCC 6538P, *Bacillus subtilis* No. 10707, *Klebsiella pneumoniae* ATCC 10031 and *Escherichia coli* ATCC 26, with MIC values of 0.11, 0.11, 0.057, 0.057 and 3.65 µg/ml, respectively. Other compounds from this series of DC-107 derivatives include the following:



Compound	R1	Formula
267959	OCH2CH2OMe	C ₂₉ H ₃₈ N ₂ O ₁₀ S ₃
267960	(OCH2CH2)4OMe	C ₃₅ H ₅₀ N ₂ O ₁₃ S ₃
267961	OCH2CH2OCH2CH2OCH2CH2OH	C ₃₂ H ₄₄ N ₂ O ₁₂ S ₃
267963	CH2OH	C ₂₇ H ₃₄ N ₂ O ₉ S ₃
267964	CH2CH2OH	C ₂₈ H ₃₆ N ₂ O ₉ S ₃



267962: C48 H65 N3 O20 S3

SOURCE – Kyowa Hakko.

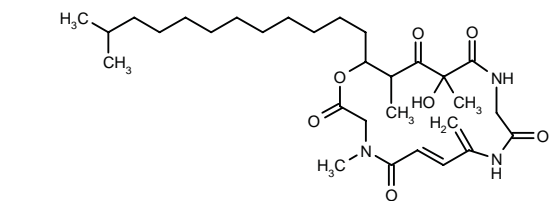
REFERENCES

1. Kanda, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *DC 107 derivs.* (2). EP 887351, WO 9825934.

BE-43547A₁

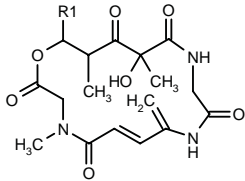
265902

14-Hydroxy-4,14,16-trimethyl-17-(11-methyldodecyl)-8-methylene-1-oxa-4,9,12-triaza-6-cycloheptadecene-2,5,10,13,15-pentaone



C30 H49 N3 O7; Mol wt: 563.7311

ACTION – Antineoplastic agent isolated from *Streptomyces* sp. A43547 (FERM p-14444), with potent *in vitro* cytotoxicity against various tumor cells such as murine leukemia P388 cells (IC₅₀ = 0.14 µg/ml) and colon 26 tumor cells (IC₅₀ = 0.032 µg/ml). Other compounds isolated from this source are:



Compound	R1	Formula
BE-43547A ₂ [266691]	C13H27	C ₃₀ H ₄₉ N ₃ O ₇
BE-43547B ₁ [266692]	(CH2)10CH(Me)Et	C ₃₁ H ₅₁ N ₃ O ₇
BE-43547B ₂ [266693]	i-Pr(CH2)11	C ₃₁ H ₅₁ N ₃ O ₇
BE-43547B ₃ [266694]	C14H29	C ₃₁ H ₅₁ N ₃ O ₇
BE-43547C ₁ [266695]	i-Pr(CH2)12	C ₃₂ H ₅₃ N ₃ O ₇
BE-43547C ₂ [266696]	C15H31	C ₃₂ H ₅₃ N ₃ O ₇

SOURCE – Banyu.

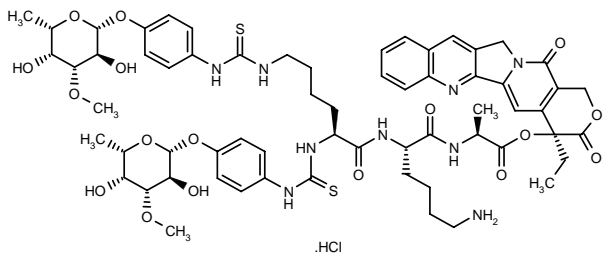
REFERENCES

1. Nishioka, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Anti tumor substances BE-43547*. JP 98147594.

DNA-INTERCALATING DRUGS

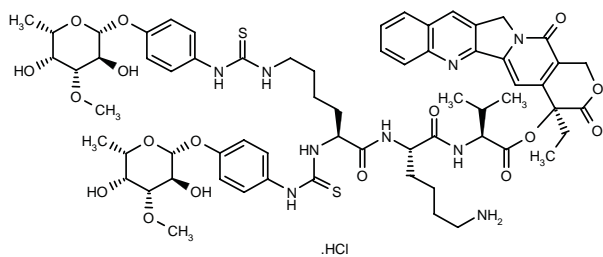
264444

4(S)-[N^α,N^ε-Bis[N-[4-(6-deoxy-3-O-methyl-β-L-galactopyranosyloxy)phenyl]thiocarbamoyl]-L-lysyl-L-lysyl-L-alanyloxy]-4-ethyl-3,4,12,14-tetrahydropyrano-[3',4':6,7]inolizino[1,2-*b*]quinoline-3,14-dione hydrochloride



C63 H79 N9 O17 S2 . HCl; Mol wt: 1334.9560

ACTION – Antineoplastic agent, a camptothecin glycoconjugate with highly improved water solubility. Compound exhibited potent *in vitro* cytotoxicity against human SW480 and HT29 and murine B16F10 tumor cells (IC₅₀ = 0.015, 0.025 and 0.1 µM, respectively), and was associated with lower hematopoietic toxicity than 20(S)-camptothecin. *In vivo*, it reduced tumor volume in nude mice inoculated with lung carcinoma LXFL 529, showing a relative tumor volume on day 14 after tumor implantation of 62% of the control value when given at 12.5 mg/kg/day i.v. x 3 days. Another compound from this series of 20-O-linked camptothecin glycoconjugates is:



266683: C65 H83 N9 O17 S2 . HCl

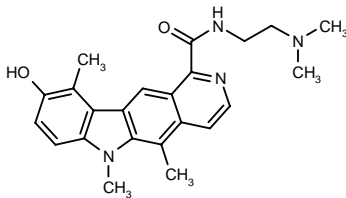
SOURCE – Bayer.

REFERENCES

1. Lerchen, H.-G. et al. (Bayer AG) *20-O-Linked camptothecin glycoconjugates*. WO 9815573.

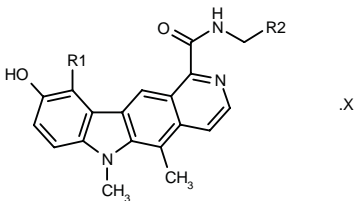
268398

N-[2-(Dimethylamino)ethyl]-9-hydroxy-5,6,10-trimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide



C23 H26 N4 O2; Mol wt: 390.4844

ACTION – Antineoplastic agent with more potent cytotoxicity than doxorubicin against murine leukemia L1210, human lung carcinoma A549, human epidermoid carcinoma KB-3-1 and multidrug-resistant KB-A1 cells, giving IC₅₀ values of 3.5, 6.5, 6.3 and 329.1 nM, respectively, compared to IC₅₀ values of 24.3, 39.8, 18.1 and 6746 nM, respectively, for doxorubicin. Other compounds from this series of ellipticine derivatives include the following:



Compound	R1	R2	X	Formula
268399	H	C(Me)2CH2-N(Me)2	2HCl	C ₂₅ H ₃₀ N ₄ O ₂ ·2HCl
268400	CH2N(Me)2	CH2N(Me)2	3HCl	C ₂₅ H ₃₁ N ₅ O ₂ ·3HCl
268401	allyl	CH2N(Me)2		C ₂₅ H ₂₈ N ₄ O ₂
268402	Pr	CH2N(Me)2		C ₂₅ H ₃₀ N ₄ O ₂

SOURCE – ADIR.

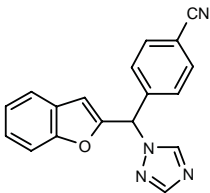
REFERENCES

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HORMONAL AGENTS

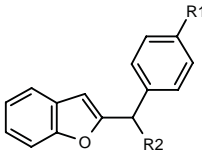
265119

4-[1-(Benzofuran-2-yl)-1-(1,2,4-triazol-1-yl)methyl]-benzonitrile



C18 H12 N4 O; Mol wt: 300.3198

ACTION – Agent for the treatment and prevention of breast, ovarian, uterine, pancreatic and endometrial cancer, as well as benign prostatic hypertrophy, with potent aromatase-inhibitory activity (IC₅₀ = 2.8 nM against enzyme from human placenta). *In vivo*, it produced significant decreases in plasma estrogen levels in female rats pretreated with pregnant mare's serum gonadotropin (PMSG) following i.v. and p.o. administration, with a duration of action of > 24 h. It was also shown to reduce uterine weight of pubertal rats stimulated with androstenedione. Within this series of specifically claimed heterocyclic furan derivatives, the following are also included:



Compound	R1	R2	Formula
267708	F	1,2,4-triazol-1-yl	C ₁₇ H ₁₂ FN ₃ O
267709	Me	1,2,4-triazol-4-yl	C ₁₈ H ₁₅ N ₃ O

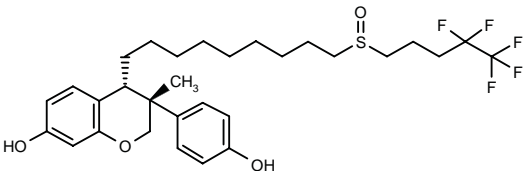
SOURCE – Menarini.

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1. Lombardi, P. and Di Pietro, G. (Menarini Industrie Farma Riunite srl) *Heterocyclic furan cpds., their preparation and use as aromatase inhibitors*. WO 9818791.

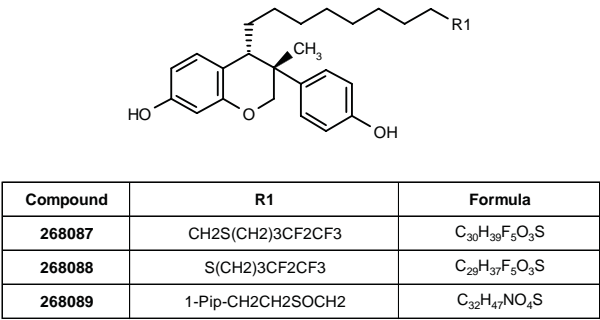
268086

(3*RS*,4*RS*)-3-(4-Hydroxyphenyl)-3-methyl-4-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]-3,4-dihydro-2*H*-1-benzopyran-7-ol



C30 H39 F5 O4 S; Mol wt: 590.6901

ACTION – Agent with good antiestrogenic activity and devoid of agonist activity, claimed for use in the treatment of estrogen-related disorders such as anovular infertility, breast cancer, endometriosis, menstrual disorders and endometrial or ovarian cancer. It gave an IC₅₀ value of 54.8 nM for inhibition of the growth of human breast adenocarcinoma MCF-7 cells. *In vivo* antiestrogenic activity was demonstrated by the ability to inhibit the increase in uterine weight in ovariectomized mice treated with 17β-estradiol (87% inhibition at 30 µg/mouse s.c. once a day for 3 days); compound exhibited similar activity after oral administration at a dose of 10 mg/kg/day x 3 days. It has little effect on bone mineral density. Within this series of specifically claimed benzopyran derivatives, the following are also included:



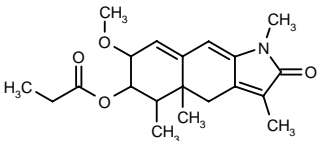
SOURCE – C & C Research.

REFERENCES

1. Jo, J.C. et al. (C & C Research Laboratories) *Novel benzopyran derivs.* WO 9825916.

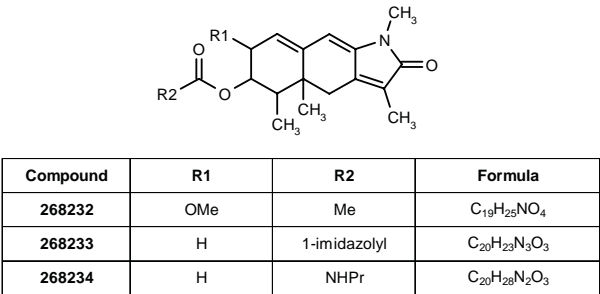
268231

7-Methoxy-1,3,4a,5-tetramethyl-6-(propionyloxy)-2,4,4a,5,6,7-hexahydro-1H-benzo[f]indol-2-one



C20 H27 N O4; Mol wt: 345.4363

ACTION – Progesterone receptor antagonist with an IC₅₀ of 17 nM against [³H]-progesterone binding in porcine uterine cell preparations vs. 106 nM for mifepristone, potentially useful in the treatment of breast and ovarian cancers, endometriosis, osteoporosis and other menopausal symptoms. Other representative compounds within this series of tetrahydrobenzindolone derivatives include the following:



SOURCE – Meiji Seika.

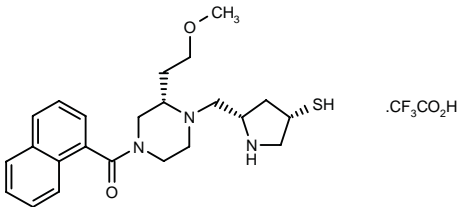
REFERENCES

1. Kurihara, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel tetrahydrobenzindolone derivs.* WO 9827059.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

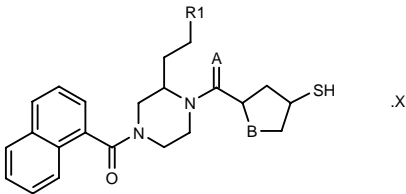
265467

[2S-[2α(R*),4α]]-2-(2-Methoxyethyl)-4-(1-naphthyl-carbonyl)-1-(4-sulfanylpyrrolidin-2-ylmethyl)piperazine trifluoroacetate

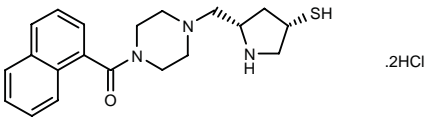


C23 H31 N3 O2 S . C2 H F3 O2; Mol wt: 527.6048

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and Ras farnesylation. Also useful for the treatment of other conditions associated with signal transduction pathways operating through Ras, as well as disorders associated with proteins other than Ras that are also posttranslationally modified by protein farnesyltransferase. Other specifically claimed compounds include the following:



Compound	R1	A	B	Isomer	X	Formula
267474	OMe	O	CH2	1S-(1α,3α)		C ₂₄ H ₃₀ N ₂ O ₃ S
267475	OMe	H2	CH2	1S-(1α,3α)	HCl	C ₂₄ H ₃₂ N ₂ O ₂ S .HCl
267476	3-Pyr- -CH2O	H2	NH	2S-[2α(R*),4α]	CF3CO2H	C ₂₈ H ₃₄ N ₄ O ₂ S .CF ₃ CO ₂ H
267477	OMe	H2	NH	2S-[2α(R*),4β]	2HCl	C ₂₃ H ₃₁ N ₃ O ₂ S .2HCl
267478	OMe	H2	NH	2R-[2α(S*),4β]	2HCl	C ₂₃ H ₃₁ N ₃ O ₂ S .2HCl
267480	SO2Ph	H2	NH	2S-[2α(R*),4α]	CF3CO2H	C ₂₈ H ₃₃ N ₃ O ₃ S ₂ .CF ₃ CO ₂ H



267479: C20 H25 N3 OS . 2HCl

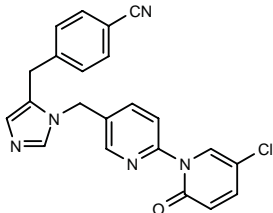
SOURCE – Rhône-Poulenc Rorer.

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1. Bourzat, J.-D. et al. (Rhône-Poulenc Rorer SA) *Farnesyl transferase inhibitors*. WO 9829390.

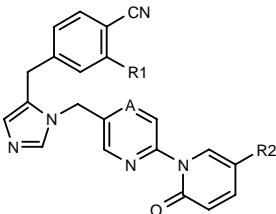
268687

4-[1-[6-(5-Chloro-2-oxo-1,2-dihydropyridin-1-yl)pyridin-3-ylmethyl]imidazol-5-ylmethyl]benzonitrile

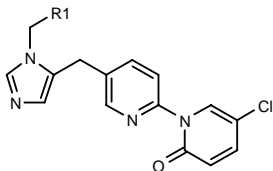


C22 H16 Cl N5 O; Mol wt: 401.8554

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase and the farnesylation of the oncogene protein Ras. Other specifically claimed compounds include the following:



Compound	R1	R2	A	Formula
268688	H	Br	CH	C ₂₂ H ₁₆ BrN ₅ O
268691	H	Cl	N	C ₂₁ H ₁₅ ClN ₅ O
268692	OMe	Cl	CH	C ₂₃ H ₁₈ ClN ₅ O ₂



Compound	R1	Formula
268689	4-CN-Ph	C ₂₂ H ₁₆ ClN ₅ O
268690	6-CN-3-Pyr	C ₂₁ H ₁₅ ClN ₆ O

SOURCE – Merck & Co.

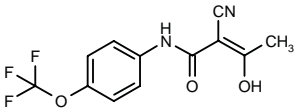
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1. Young, S.D. et al. (Merck & Co., Inc.) *Inhibitors of farnesyl-protein transferase*. WO 9829119.

LFM-A12

267508

(Z)-2-Cyano-3-hydroxy-N-[4-(trifluoromethoxy)phenyl]-2-butenamide



C12 H9 F3 N2 O3; Mol wt: 286.2081

ACTION – Specific inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase, an analog of leflunomide reported to kill over 99% of breast cancer cells in a clonogenic assay (IC₅₀ = 1.7 μM). It is able to kill multidrug-resistant and radiation-resistant human breast cancer cells and prevent them from invading and migrating through tissues. The compound was well tolerated in animal studies and is expected to be useful as a treatment for most forms of breast cancer independent of the level of estrogen receptor expression, and also in combination regimens to reduce the need for very-high-dose chemotherapy by enhancing the sensitivity of cancer cells to chemotherapeutic drugs.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

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- Bartlett, R.R. and Kämmerer, F.-J. (Hoechst AG) *Isoxazole-4-carboxamides and hydroxyalkylidene-cyanoacetamides, drugs containing these cpds. and use of such drugs*. EP 527736, JP 93506425, US 5494911, US 5532259, WO 9117748.
- Ghosh, S. et al. *α-Cyano-β-hydroxy-β-methyl-N-[4-(trifluoromethoxy)-phenyl]propenamide: An inhibitor of the epidermal growth factor receptor tyrosine kinase with potent cytotoxic activity*. Clin Cancer Res 1998, 4(11): 2657.
- Zheng, Y. et al. *Novel leflunomide analogs as potent anti-breast cancer agents*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 343.
- Wayne Hughes Institute develops potent new agent for breast cancer. Prous Science Daily Essentials 1998, Oct 16.

ANTANGIOGENIC AGENTS

265903

H-Thr-Glu-Ala-Thr-Ile-Thr-Gly-Leu-Glu-Pro-Gly-Thr-Glu-Tyr-Thr-Ile-Tyr-Val-Ile-Ala-Leu-OH

C103 H163 N21 O35; Mol wt: 2255.5330

ACTION – Peptide with cell adhesion-inhibitory properties (71% inhibition at 200 μg/ml in A375 melanoma cell preparations), potentially useful for the treatment of tumor metastasis.

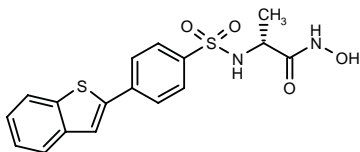
SOURCE – Hisamitsu.

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1. Fukai, F. and Katayama, T. (Hisamitsu Pharmaceutical Co., Ltd.) *Bioactive peptides and cancer metastasis inhibitors*. JP 98147600.

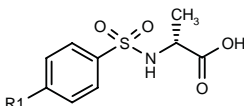
267940

2(R)-[4-(Benzothien-2-yl)phenylsulfonamido]propionohydroxamic acid



C17 H16 N2 O4 S2; Mol wt: 376.4554

ACTION – An inhibitor of matrix metalloproteinases such as gelatinase A (IC_{50} = 0.30 μ M against enzyme purified from human dermal fibroblasts) with potential in the treatment of tumor growth and metastasis, rheumatoid arthritis, osteoarthritis, periodontal disease, osteoporosis, nephritis, arteriosclerosis, pulmonary emphysema, hepatic cirrhosis, corneal injury and autoimmune diseases. Other compounds from this series of phenylsulfonamide derivatives are:



Compound	R1	Formula
267941	2-indolyl	C ₁₇ H ₁₆ N ₂ O ₄ S
267942	2-benzoxazolyl	C ₁₆ H ₁₄ N ₂ O ₅ S
267943	2-benzothieryl	C ₁₇ H ₁₅ NO ₄ S ₂
267944	5-Me-2-benzoxazolyl	C ₁₇ H ₁₆ N ₂ O ₅ S
267945	5-Me-2-benzofuryl	C ₁₈ H ₁₇ NO ₅ S

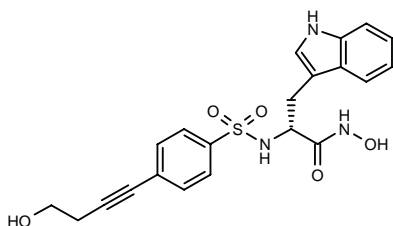
SOURCE – Ono.

REFERENCES

1. Takahashi, K. and Sugiura, T. (Ono Pharmaceutical Co., Ltd.) *Phenylsulfonamido derivs.* JP 98204059.

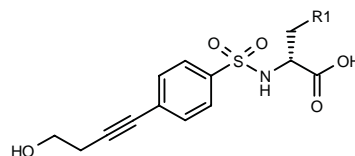
267966

2(R)-[4-(4-Hydroxy-1-butynyl)phenylsulfonamido]-3-(1H-indol-3-yl)propionohydroxamic acid



C21 H21 N3 O5 S; Mol wt: 427.4789

ACTION – An inhibitor of matrix metalloproteinases such as gelatinase A and collagenase (IC_{50} = 0.00042 and 0.26 μ M, respectively, against enzymes purified from human dermal fibroblasts) with potential in the treatment of tumor growth and metastasis, rheumatoid arthritis, osteoarthritis, periodontal disease, osteoporosis, nephritis, arteriosclerosis, pulmonary emphysema, hepatic cirrhosis, corneal injury and autoimmune diseases. Other compounds from this series of phenylsulfonamide derivatives include the following:



Compound	R1	Formula
267967	3-indolyl	C ₂₁ H ₂₀ N ₂ O ₅ S
267968	CH ₂ CON(Me)CH ₂ CH ₂ Ph	C ₂₄ H ₂₈ N ₂ O ₆ S

SOURCE – Ono.

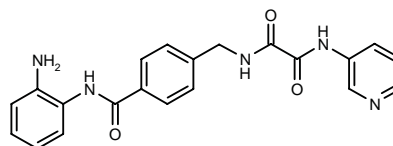
REFERENCES

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MISCELLANEOUS ANTINEOPLASTIC DRUGS

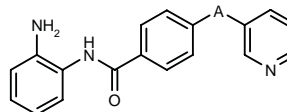
265432

N-(2-Aminophenyl)-4-[N-(3-pyridyl)oxamoylaminomethyl]-benzamide



C21 H19 N5 O3; Mol wt: 389.4131

ACTION – Antineoplastic agent with potent differentiation-inducing activity in human colon cancer A2780 cells, as determined by its ability to increase alkaline phosphatase activity (minimum effective concentration = 0.003 μ M). It prolonged survival time in mice inoculated with murine myeloid leukemia WEHI-3 cells (T/C x 100 = 138% at 16 μ mol/kg p.o. on days 1-4 and 7-11 after tumor inoculation). Other specifically claimed benzamide derivatives include the following:



Compound	A	Formula
266686	-CH ₂ NHCO ₂ CH ₂ -	C ₂₁ H ₂₀ N ₄ O ₃
266687	-CH ₂ NHCOCH ₂ O-	C ₂₁ H ₂₀ N ₄ O ₃
266688	-NHCOCH ₂ OCH ₂ -	C ₂₁ H ₂₀ N ₄ O ₃

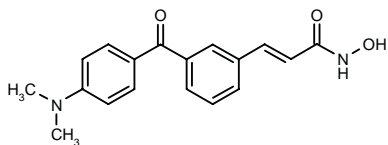
SOURCE – Mitsui Chemicals.

REFERENCES

1. Suzuki, T. et al. (Mitsui Chemicals, Inc.) *Benzamide derivs., useful as cell differentiation inducers.* EP 847992.

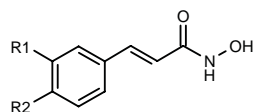
267834

3-[3-[4-(Dimethylamino)benzoyl]phenyl]-2(*E*)-propeno-hydroxamic acid

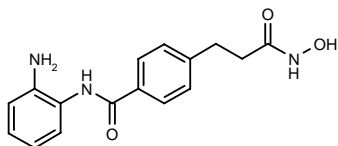


C₁₈ H₁₈ N₂ O₃; Mol wt: 310.3512

ACTION – Cancer cell differentiating-inducing agent found to be 10,000-fold more potent than sodium acetate in inducing differentiation in human ovarian cancer A2780 cells. Other compounds from this series of hydroxamic acid derivatives include the following:



Compound	R1	R2	Formula
267835	COPh	H	C ₁₆ H ₁₃ NO ₃
267836	H	4-N(Me)2-PhCO	C ₁₈ H ₁₈ N ₂ O ₃
267837	H	Ph	C ₁₅ H ₁₃ NO ₂



267838: C₁₆ H₁₇ N₃ O₃

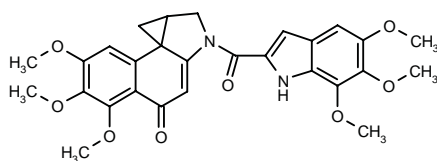
SOURCE – Mitsui Chemicals.

REFERENCES

1. Suzuki, T. et al. (Mitsui Pharmaceuticals Inc.) *Novel hydroxamic acid derivs.* JP 98182583.

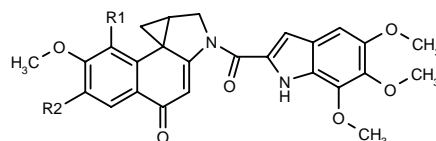
268160

5,6,7-Trimethoxy-2-(5,6,7-trimethoxy-1*H*-indol-2-yl)-carbonyl)-2,4,9,9a-tetrahydro-1*H*-benzo[*e*]cycloprop[*c*]indol-4-one

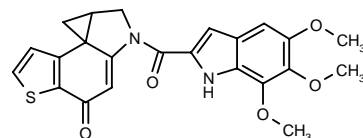


C₂₈ H₂₈ N₂ O₈; Mol wt: 520.5352

ACTION – Antineoplastic agent with potent *in vitro* cytotoxic activity against various tumor cells such as human lung tumor A549 cells (IC₅₀ = 0.0055 ng/ml), human colon tumor HT-29 cells (IC₅₀ = 0.0015 ng/ml) and human nasal cancer KB3-1 cells (IC₅₀ = 0.008 ng/ml). A particularly potent compound within a series of cytotoxic substances, wherein the following are also included:



Compound	R1	R2	Formula
268162	OMe	OMe	C ₂₈ H ₂₈ N ₂ O ₈
268164	H	NHAc	C ₂₈ H ₂₇ N ₃ O ₇
268165	H	N(Me)CH ₂ CH ₂ OH	C ₂₉ H ₃₁ N ₃ O ₇
268166	H	OCH ₂ CH ₂ OH	C ₂₈ H ₂₈ N ₂ O ₈



268163: C₂₃ H₂₀ N₂ O₅ S

SOURCE – Shionogi.

REFERENCES

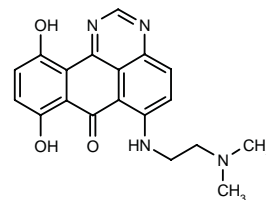
1. Natsume, M. et al. (Shionogi & Co. Ltd.) *Cpds. having antitumor activity.* WO 9825900.

BP-1

268093

6-[2-(Dimethylamino)ethylamino]-8,11-dihydroxy-7*H*-benzo[*e*]perimidin-7-one

NSC-669967



C₁₉ H₁₈ N₄ O₃; Mol wt: 350.3762

ACTION – Antineoplastic agent with potent cytotoxic activity against a broad spectrum of human tumor cells including doxorubicin-resistant human adenocarcinoma LoVo (LoVo/Dx) cells (EC₅₀ = 0.0049 ± 0.0008 µg/ml) and a series of human leukemia and renal cancer cell lines, non-small cell lung cancer A549 and breast cancer MCF-7 cell lines (GI₅₀ < 0.01 µM). It was active *in vivo* in prolonging survival in mice inoculated with murine leukemia P388 cells (T/C x 100 = 155% at 0.5 mg/kg/day x 5 days i.p.). A representative compound within a series of 6-[(aminoalkyl)amino]-7*H*-benzo[*e*]perimidin-7-one derivatives.

SOURCE – Politechnika Gdanska, Gdansk (PL).

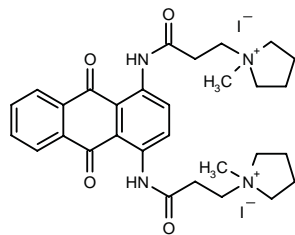
REFERENCES

1. Borowski, E. (Politechnika Gdanska) *New derivs. of 6-[(aminoalkyl)amino]-7H-benzo[e]-perimidin-7-one, method of their preparation, and their use as a medicament.* WO 9825910.

BSU-1075

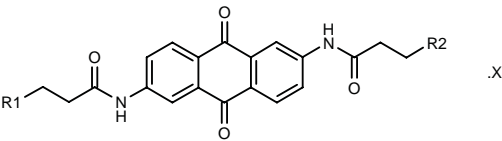
267765

1,4-Bis[3-(1-methylpyrrolidinium-1-yl)propionamido]-9,10-anthraquinone diiodide

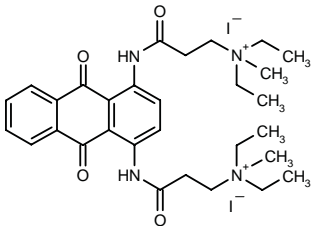


C30 H38 I2 N4 O4 ; Mol wt: 772.4542

ACTION – Antineoplastic agent, an inhibitor of telomerase activity, as demonstrated using standard telomerase protein extract from human ovarian carcinoma A2780 cells (IC₅₀ = 5.0 μM). Within this series of specifically claimed anthraquinone derivatives, the following are also included:



Compound	R1=R2	X	Formula
BSU-1061 [267766]	N(Me)3 ⁺	diiodide	C ₂₆ H ₃₄ I ₂ N ₄ O ₄
BSU-1041 [267767]	N(CH ₂ CH ₂ OH)2		C ₂₈ H ₃₈ N ₄ O ₈



BSU-1073 [267768]: C30 H42 I2 N4 O4

SOURCES – Cancer Research Campaign Technology; University of Texas System, Austin, TX (US).

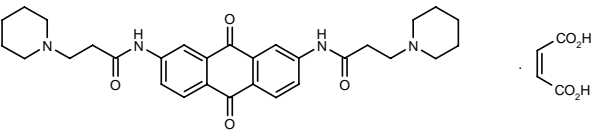
REFERENCES

1. Neidle, S. et al. (Cancer Research Campaign Technology Ltd.;University of Texas System) *Anthraquinones with biological activity*. WO 9825885.

BSU-9057

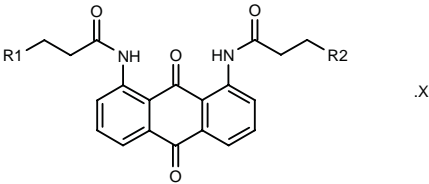
267769

2,7-Bis[3-(1-piperidiny)l)propionamido]-9,10-anthraquin-one maleate

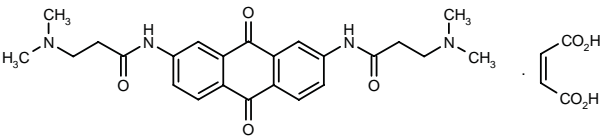


C30 H36 N4 O4 . C4 H4 O4; Mol wt: 632.7100

ACTION – Antineoplastic agent that acts by virtue of its telomerase-inhibitory activity (IC₅₀ = 0.1 μM using telomerase protein extract from human ovarian carcinoma A2780 cells). Within this series of specifically claimed anthraquinone derivatives, the following are also included:



Compound	R1=R2	X	Formula
BSU-9051 [267770]	N(Me)2	fumarate	C ₂₄ H ₂₈ N ₄ O ₄ .C ₄ H ₄ O ₄
BSU-9052 [267771]	N(Me)3 ⁺	diiodide	C ₂₆ H ₃₄ I ₂ N ₄ O ₄
BSU-9054 [267772]	N(Et)2	fumarate	C ₂₈ H ₃₆ N ₄ O ₄ .C ₄ H ₄ O ₄



BSU-9066 [267773]: C24 H28 N4 O4 . C4 H4 O4

SOURCE – Cancer Research Campaign Technology.

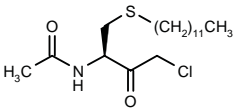
REFERENCES

1. Neidle, S. et al. (Cancer Research Campaign Technology Ltd.) *Further anthraquinones with biological activity*. WO 9825884.

DDE-131

267569

N-[3-Chloro-1 (R)-(dodecylsulfanylmethyl)-2-oxo-propyl]acetamide



C18 H34 Cl N O2 S; Mol wt: 363.9906

ACTION – Antineoplastic agent, a chloromethyl ketone derivative proven to exert cytotoxic activity against human breast and prostate cancer cell lines and to induce apoptotic cell death in multidrug-resistant human breast cancer cells.

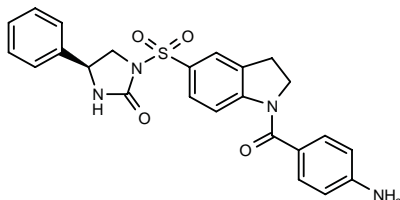
SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

REFERENCES

1. Perrey, D.A. et al. *Chloromethyl ketone derivatives induce apoptosis in multi-drug resistant human breast cancer cells*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 345.

DW-2282***267148****263991** (as hydrochloride)

(+)-(S)-1-[1-(4-Aminobenzoyl)indolin-5-ylsulfonyl]-4-phenylimidazolidin-2-one



C₂₄ H₂₂ N₄ O₄ S; Mol wt: 462.5278

ACTION – Antineoplastic agent, the active S-(+)-isomer of DW-2143⁺ proven to have high cytotoxic activity against human lung carcinoma A-549, human chronic myelogenous leukemia K562 and human ovarian adenocarcinoma SK-OV-3 cells (IC₅₀ = 0.21, 1.66 and 0.12 μM, respectively, vs. 0.45, 2.60 and 0.21 μM, respectively, for DW-2143) *in vitro*, as well as high activity against human colon carcinoma SW620 xenografts in mice.

SOURCE – Dong-Wha.

REFERENCES

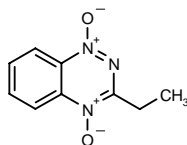
1. Yoon, S.J. et al. (Dong-Wha Pharmaceutical Industry Co. Ltd.) *Arylsulfonyl-imidazolidinone derivatives as an antitumor agent*. WO 9807719.
2. Jung, S.-H. et al. *Synthesis and oncolytic activity of 4-phenyl-1-arylsulfonyl imidazolidinones: Powerful antitumor effect of DW 2282*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 330.

*Identified compound **263991** (see **263304**) Drug Data Report 1998, 020(06): 0546.

*Drug Data Report 1998, 020(08): 0724.

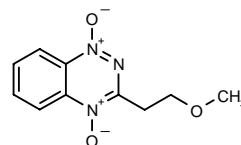
SR-4895¹⁻³**267816**

3-Ethyl-1,2,4-benzotriazine-1,4-dioxide



C₉ H₉ N₃ O₂; Mol wt: 191.1891

ACTION – Antineoplastic agent, a hypoxic cytotoxin derived from tirapazamine with almost equivalent *in vitro* hypoxic cytotoxicity and activity in fractionated irradiation studies in SCCVII tumor-bearing mice, but with superior physicochemical properties, making it a potential backup candidate to tirapazamine; it was also equivalent to tirapazamine as a modifier of cisplatin antitumor activity. Another promising compound from this series of 1,2,4-benzotriazine 1,4-dioxides is:



SR-4941 [267817]^{1,2}: C₁₀ H₁₁ N₃ O₃

SOURCE – SRI.

REFERENCES

1. Brown, M.J. (Leland Stanford Junior University) *Method of tumor treatment*. EP 649658.
2. Kelson, A.B. et al. *1,2,4-Benzotriazine 1,4-dioxides. An important class of hypoxic cytotoxins with antitumor activity*. *Anti-Cancer Drug Des* 1998, 13(6): 575.
3. Wardman, P. et al. *Chemical properties which control selectivity and efficacy of aromatic N-oxide bioreductive drugs*. *Br J Cancer* 1996, 74(Suppl. 27): S70.

CANCER GENE THERAPY
rAd/p21**266562**

Recombinant adenovirus encoding human p21^{WAF1} (p21) gene

ACTION – Cancer gene therapy consisting of a replication-defective recombinant adenoviral system (rAd) and the tumor suppressor gene p21^{WAF1}, a cyclin-dependent kinase inhibitor induced by p53 upon DNA damage or p53 overexpression, resulting in cell cycle arrest at the G1 phase and inhibition of further cell proliferation. *In vitro*, the gene therapy was found to inhibit human pancreatic adenocarcinoma HPAC and Hs766T cell growth, with an increase in the number of cells in G0/G1, as well as to induce a significant increase in p21 protein expression. Other *in vitro* studies showed concentration-dependent p21 induction and cell growth inhibition in human non-small cell lung cancer NCI-H460 and NCI-H322 cell lines after rAd/p21 infection, which again appeared to be due to G0/G1 arrest. In SCID mice bearing NCI-H460 tumors, repeated intraumoral delivery of rAd/p21 significantly suppressed tumor growth and prolonged survival.

SOURCES – Harper Hospital, Detroit, MI (US); Karmanos Cancer Institute, Detroit, MI (US); Wayne State University, Detroit, MI (US).

REFERENCES

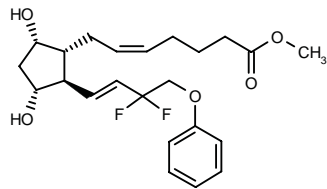
1. Joshi, U.S. et al. *Inhibition of pancreatic tumor cell growth in culture by p21^{WAF1} recombinant adenovirus*. *Pancreas* 1998, 16(2): 107.
2. Joshi, U.S. et al. *Inhibition of tumor cell growth by p21^{WAF1} adenoviral gene transfer in lung cancer*. *Cancer Gene Ther* 1998, 5(3): 183.

OCULAR MEDICATIONS

ANTIGLAUCOMA AGENTS

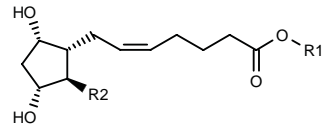
268408

15-Deoxy-15,15-difluoro-16-phenoxy-17,18,19,20-tetranorprostaglandin F_{2α} methyl ester



C₂₃ H₃₀ F₂ O₅; Mol wt: 424.4810

ACTION – Fluorinated prostaglandin F_{2α} (PGF_{2α}) derivative with superior intraocular pressure-lowering activity and a longer duration of action compared to the parent compound, and which causes negligible eye irritation or damage to the cornea, iris or conjunctiva and has little effect on melanogenesis compared to latanoprost. Other compounds from this series of difluoroprostaglandin derivatives are:



Compound	R1	R2	Formula
268409	Me	(E)-3-Cl-PhOCH ₂ CF ₂ CH=CH	C ₂₃ H ₂₉ ClF ₂ O ₅
268410	Me	CH ₂ CH ₂ CF ₂ CH ₂ OPh	C ₂₃ H ₃₂ F ₂ O ₅
268411	i-Pr	(E)-CH=CHCF ₂ CH ₂ OPh	C ₂₅ H ₃₄ F ₂ O ₅

SOURCES – Asahi Glass; Santen.

REFERENCES

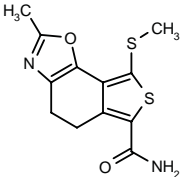
1. Shirasawa, E. et al. (Asahi Glass Co., Ltd.;Santen Pharmaceutical Co., Ltd.) Difluoroprostaglandin derivs. and their use. EP 850926.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

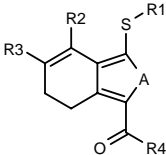
265244

2-Methyl-8-(methylsulfanyl)-4,5-dihydrothieno[3,4-*g*]-benzoxazole-6-carboxamide



C₁₂ H₁₂ N₂ O₂ S₂; Mol wt: 280.3708

ACTION – Agent for the treatment of osteoporosis that acts by promoting osteogenesis and inhibiting collagenase activity; at a concentration of 10 μM, compound caused a marked increase in alkaline phosphatase activity in rat femoral bone marrow stromal cells. Other condensed heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
267586	Me	-N=C(Ph)S-		NH ₂ t	S	C ₁₉ H ₁₈ N ₂ O ₃
267587	Me	-N=C(Ph)S-		1,3-benzodioxol-5-yl-CH ₂ NH	S	C ₂₅ H ₂₀ N ₂ O ₃ S ₃
267588	Me	-N=C(Ph)S-		4-Pyr-CH ₂ NH	S	C ₂₃ H ₁₉ N ₃ O ₃
267589	Me	-N=C(Ph)S-		3-Pyr-NH	S	C ₂₂ H ₁₇ N ₃ O ₃
267590	Me	-N=C(Ph)S-		N(Me)OMe	S	C ₁₉ H ₁₈ N ₂ O ₂ S ₃
267591	Me	-N=C(Me)S-		NH ₂	S	C ₁₂ H ₁₂ N ₂ O ₃
267592	i-Pr	-OC(Me)=N-		NH ₂	S	C ₁₄ H ₁₆ N ₂ O ₂ S ₂
267593	Me	-N=C(Ph)S-		OH	O	C ₁₇ H ₁₃ NO ₃ S ₂

SOURCE – Takeda.

REFERENCES

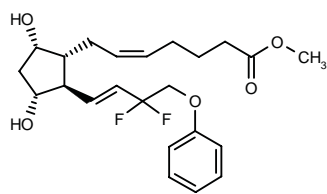
1. Yasuma, T. et al. (Takeda Chemical Industries, Ltd.) Condensed heterocyclic derivs., their preparation method and their use. JP 98130271.

OCULAR MEDICATIONS

ANTIGLAUCOMA AGENTS

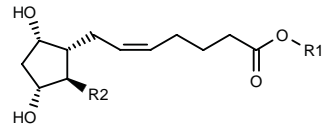
268408

15-Deoxy-15,15-difluoro-16-phenoxy-17,18,19,20-tetranorprostaglandin F_{2α} methyl ester



C23 H30 F2 O5; Mol wt: 424.4810

ACTION – Fluorinated prostaglandin F_{2α} (PGF_{2α}) derivative with superior intraocular pressure-lowering activity and a longer duration of action compared to the parent compound, and which causes negligible eye irritation or damage to the cornea, iris or conjunctiva and has little effect on melanogenesis compared to latanoprost. Other compounds from this series of difluoroprostaglandin derivatives are:



Compound	R1	R2	Formula
268409	Me	(E)-3-Cl-PhOCH2CF2CH=CH	C ₂₃ H ₂₉ ClF ₂ O ₅
268410	Me	CH2CH2CF2CH2OPh	C ₂₃ H ₃₂ F ₂ O ₅
268411	i-Pr	(E)-CH=CHCF2CH2OPh	C ₂₅ H ₃₄ F ₂ O ₅

SOURCES – Asahi Glass; Santen.

REFERENCES

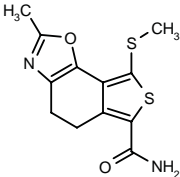
1. Shirasawa, E. et al. (Asahi Glass Co., Ltd.;Santen Pharmaceutical Co., Ltd.) Difluoroprostaglandin derivs. and their use. EP 850926.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

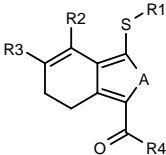
265244

2-Methyl-8-(methylsulfanyl)-4,5-dihydrothieno[3,4-*g*]-benzoxazole-6-carboxamide



C12 H12 N2 O2 S2; Mol wt: 280.3708

ACTION – Agent for the treatment of osteoporosis that acts by promoting osteogenesis and inhibiting collagenase activity; at a concentration of 10 μM, compound caused a marked increase in alkaline phosphatase activity in rat femoral bone marrow stromal cells. Other condensed heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
267586	Me	-N=C(Ph)S-		NH ₂ t	S	C ₁₉ H ₁₈ N ₂ OS ₃
267587	Me	-N=C(Ph)S-		1,3-benzodioxol-5-yl-CH ₂ NH	S	C ₂₅ H ₂₀ N ₂ O ₃ S ₃
267588	Me	-N=C(Ph)S-		4-Pyr-CH ₂ NH	S	C ₂₃ H ₁₉ N ₃ OS ₃
267589	Me	-N=C(Ph)S-		3-Pyr-NH	S	C ₂₂ H ₁₇ N ₃ OS ₃
267590	Me	-N=C(Ph)S-		N(Me)OMe	S	C ₁₉ H ₁₈ N ₂ O ₂ S ₃
267591	Me	-N=C(Me)S-		NH ₂	S	C ₁₂ H ₁₂ N ₂ OS ₃
267592	i-Pr	-OC(Me)=N-		NH ₂	S	C ₁₄ H ₁₆ N ₂ O ₂ S ₂
267593	Me	-N=C(Ph)S-		OH	O	C ₁₇ H ₁₃ NO ₃ S ₂

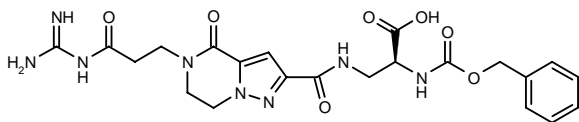
SOURCE – Takeda.

REFERENCES

1. Yasuma, T. et al. (Takeda Chemical Industries, Ltd.) Condensed heterocyclic derivs., their preparation method and their use. JP 98130271.

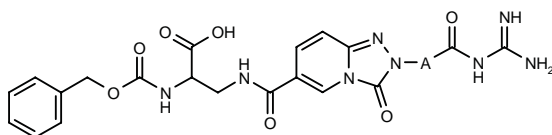
268340

2(S)-(Benzyloxycarbonylamino)-3-[5-(3-guanidino-3-oxopropyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylcarboxamido]propionic acid

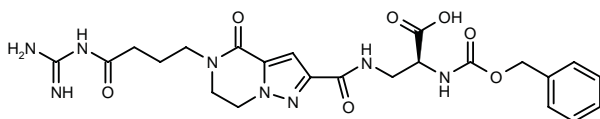


C22 H26 N8 O7; Mol wt: 514.4964

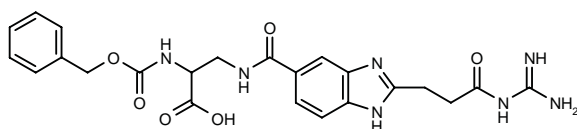
ACTION – Vitronectin receptor antagonist claimed for the treatment of osteoporosis, cancer, inflammation, cardiovascular disorders, nephropathies and retinopathies. Other exemplified compounds include the following:



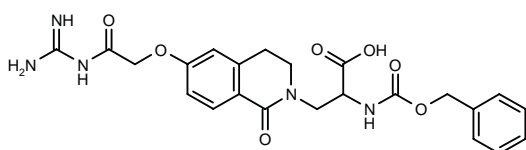
Compound	A	Formula
268342	-CH2-	C ₂₁ H ₂₂ N ₈ O ₇
268344	-(CH2)2-	C ₂₂ H ₂₄ N ₈ O ₇
268345	-(CH2)3-	C ₂₃ H ₂₆ N ₈ O ₇



268341: C23 H28 N8 O7



268343: C23 H25 N7 O6



268346: C23 H25 N5 O7

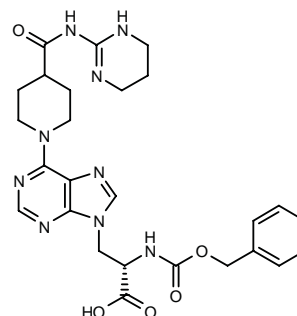
SOURCES – Genentech; Hoechst Marion Roussel.

REFERENCES

1. Wehner, V. et al. (Hoechst AG;Genentech, Inc.) *Vitronectin receptor antagonists, their production and their use*. EP 854140.

268359

2(S)-(Benzyloxycarbonylamino)-3-[6-[4-[N-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]piperidin-1-yl]purin-9-yl]propionic acid



C26 H31 N9 O5; Mol wt: 549.5889

ACTION – Agent for the treatment of osteoporosis with bone resorption-inhibitory activity that acts as a vitronectin ($\alpha_v\beta_3$) receptor antagonist ($IC_{50} = 0.004 \mu M$). A specifically claimed compound within a series of substituted purine derivatives.

SOURCES – Genentech; Hoechst Marion Roussel.

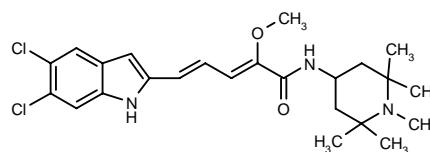
REFERENCES

1. Peyman, A. et al. (Hoechst AG;Genentech, Inc.) *Subst. purine derivs. as vitronectin receptor antagonists*. EP 853084.

SB-242784

267681

(2Z,4E)-5-(5,6-Dichloro-1H-indol-2-yl)-2-methoxy-N-(1,2,2,6,6-pentamethylpiperidin-4-yl)-2,4-pentadienamide



C24 H31 Cl2 N3 O2; Mol wt: 464.4339

ACTION – Agent for the treatment of osteoporosis, a bone resorption inhibitor that acts by potently and selectively inhibiting osteoclast vacuolar H^+ -ATPase (V-ATPase; $IC_{50} = 26 \text{ nM}$ in chicken osteoclast membranes). Reported to prevent bone resorption by human osteoclasts *in vitro* at low nanomolar concentrations and to be able to prevent bone resorption in animal models of postmenopausal osteoporosis.

SOURCE – SmithKline Beecham.

REFERENCES

1. Farina, C. et al. *Novel and selective inhibitors of the osteoclast vacuolar H^+ -ATPase with bone antiresorptive activity*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.63.

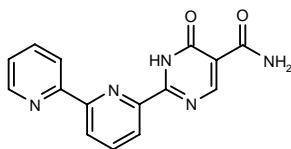
2. Gagliardi, S. et al. *Optimisation of the aminoamidic moiety in (2Z,4E) 5-(5,6-dichloro-2-indolyl)-2-methoxy-2,4-pentadienamides*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.87.

TREATMENT OF LIPOPROTEIN DISORDERS

267520

4-Oxo-2-[6-(2-pyridyl)pyridin-2-yl]-3,4-dihydropyrimidine-5-carboxamide

2-(2,2'-Bipyridin-6-yl)-4-oxo-3,4-dihydropyrimidine-5-carboxamide



C15 H11 N5 O2; Mol wt: 293.2849

ACTION – Hypolipidemic agent able to upregulate the LDL receptor *in vitro* and proven to reduce plasma cholesterol by 25% at a dose of 30 mg/kg orally for 7 days in hamsters fed a normal chow diet.

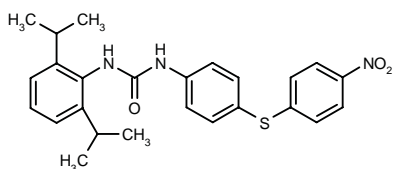
SOURCE – Pfizer.

REFERENCES

1. Chang, G. et al. *Evaluation of pyrimidones as upregulators of the low density lipoprotein (LDL) receptor*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MED1 067.

267808

N-(2,6-Diisopropylphenyl)-*N'*-[4-(4-nitrophenylsulfanyl)-phenyl]urea



C25 H27 N3 O3 S; Mol wt: 449.5723

ACTION – Potent ACAT inhibitor (IC_{50} = 0.12 and 0.58 μ M, respectively, for rat liver and rabbit intestine microsomal enzyme) found to have comparable hypolipidemic activity to DuP-128 and CI-976 in cholesterol-fed hamsters, significantly reducing total cholesterol and LDL cholesterol in serum, and total cholesterol and cholesterol esters in liver at a dose of 50 mg/kg p.o.

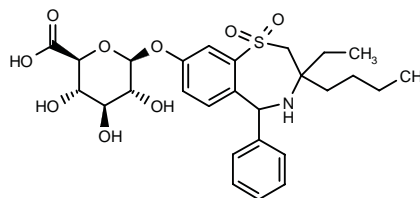
SOURCE – Slovakofarma.

REFERENCES

1. Oremus, V. et al. *Novel potent inhibitors of acyl coenzyme A:cholesterol acyl transferase substituted amides of 4-oxo-4H-1-benzopyran-2-carboxylic acid and 1,3-disubstituted ureas*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.298.

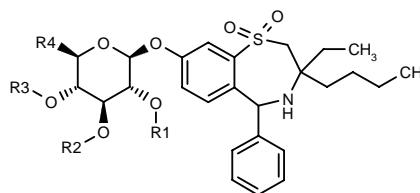
268568

1-*O*-(3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl)- β -D-glucopyranuronic acid *S,S*-dioxide

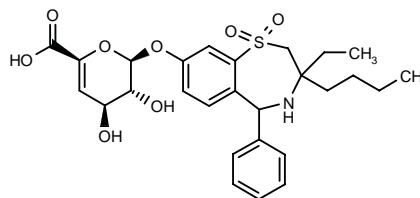


C27 H35 N O9 S; Mol wt: 549.6375

ACTION – Agent for the treatment of hyperlipidemia and atherosclerosis, an inhibitor of bile acid transport. *In vitro*, compound inhibited Na^+ -dependent [24- ^{14}C]-taurocholic acid uptake into CHO cells expressing the rabbit ileal transporter with an IC_{50} value of 70 nM. Other compounds from this series of 1,4-benzothiazepines include the following:



Compound	R1=R2=R3	R4	Formula
268569	Ac	CO2Me	C ₃₄ H ₄₃ NO ₁₂ S
268571	Ac	CH2OAc	C ₃₅ H ₄₅ NO ₁₂ S
268572	H	CH2OH	C ₂₇ H ₃₇ NO ₉ S



268570: C27 H33 N O8 S

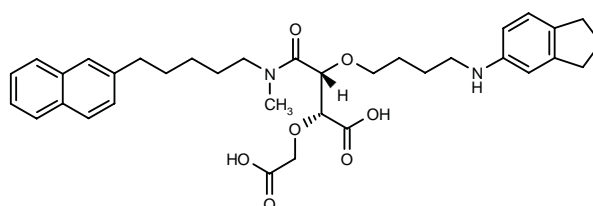
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Enhsen, A. et al. (Hoechst AG) *Hypolipidemic 1,4-benzothiazepine-1,-dioxides*. EP 864582, JP 98279568.

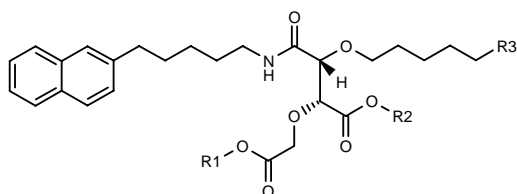
268815

2(*R*)-(Carboxymethoxy)-3(*R*)-[4-(indan-5-ylamino)-butoxy]-*N*-methyl-*N*-[5-(2-naphthyl)pentyl]succinamic acid



C35 H44 N2 O7; Mol wt: 604.7396

ACTION – Hypolipidemic agent, a squalene synthase inhibitor proven to inhibit cholesterol biosynthesis in rat liver cells with an IC_{50} of 19 μ M. Within this series of substituted propionyl derivatives, the following are also included:



Compound	R1=R2	R3	Formula
268816	H	2-Naph	C ₃₆ H ₄₁ NO ₇
268817	Na ⁺	2-benzoxazolyl	C ₃₃ H ₃₆ N ₂ Na ₂ O ₈

SOURCE – Daiichi Pharmaceutical.

REFERENCES

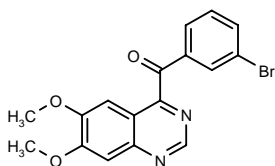
1. Usui, H. et al. (Daiichi Pharmaceutical Co., Ltd.) *Substd. propionyl derivs.* WO 9829380.

WHI-164

267444

(3-Bromophenyl)(6,7-dimethoxy-4-quinazoliny)-methanone

4-(3-Bromobenzoyl)-6,7-dimethoxyquinazoline



C₁₇ H₁₃ Br N₂ O₃; Mol wt: 373.2047

ACTION – Hypolipidemic agent proven to reduce total cholesterol and VLDL cholesterol levels 23 and 42%, respectively, at a dose of 1.6 mg/kg/day in mice fed a high-fat, high-cholesterol diet; at a dose of 8 mg/kg/day, it reduced total cholesterol and VLDL cholesterol levels by 34 and 63%, respectively, in hypercholesterolemic apolipoprotein E-deficient mice.

SOURCE – Wayne Hughes Institute, St. Paul, MN (US).

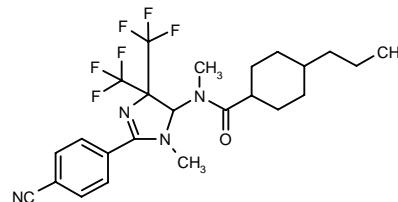
REFERENCES

1. Trieu, V.N. et al. *A novel lipid lowering agent.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 287.

XJ-304

267511

N-[2-(4-Cyanophenyl)-1-methyl-4,4-bis(trifluoromethyl)-4,5-dihydro-1*H*-imidazol-5-yl]-*N*-methyl-4-propylcyclohexanecarboxamide



C₂₄ H₂₈ F₆ N₄ O; Mol wt: 502.5002

ACTION – Potent ACAT inhibitor from a series of 4,4-bis(trifluoromethyl)imidazolines, giving IC_{50} values in the *in vitro* ACAT assay and the J774 macrophage assay of 0.09 and 2.5 μ M, respectively. Its activity was shown to reside mainly in the (–)-enantiomer. Potentially useful for the treatment of hypercholesterolemia and atherosclerosis.

SOURCE – DuPont Pharmaceuticals.

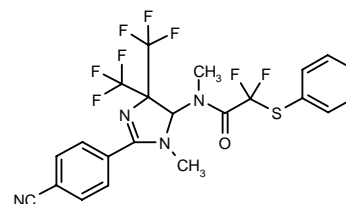
REFERENCES

1. Li, H.-Y. et al. *Design, synthesis and structure-activity relationship studies of novel 4,4-bis(trifluoromethyl)imidazolines as acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors and antihypercholesterolemic agents.* Bioorg Med Chem 1997, 5(7): 1345.
2. Li, H.-Y. et al. *Design and synthesis of novel ureas linked to 4,4-bis(trifluoromethyl)imidazolines as ACAT inhibitors.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 069.

XP-368²

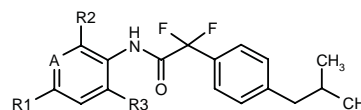
267512

N-[2-(4-Cyanophenyl)-1-methyl-4,4-bis(trifluoromethyl)-4,5-dihydro-1*H*-imidazol-5-yl]-2,2-difluoro-*N*-methyl-2-(phenylsulfanyl)acetamide



C₂₂ H₁₆ F₈ N₄ O S; Mol wt: 536.4454

ACTION – ACAT inhibitor from a series of α,α -difluoroacetamides and α,α -difluoro- α -thioacetamides designed as surrogates of transition-state analogs, wherein the following are also included:



Compound	R1	R2=R3	A	Formula
XQ-786 [267513] ^{1,2}	Me	SMe	N	C ₂₀ H ₂₄ F ₂ N ₂ OS ₂
XR-592 [267514] ²	H	i-Pr	CH	C ₂₄ H ₃₁ F ₂ NO

SOURCE – DuPont Pharmaceuticals.

REFERENCES

1. Ko, S.S. et al. (The Du Pont Merck Pharmaceutical Co.) *Amides for the treatment of atherosclerosis*. US 5583147.

2. Li, H.-Y. et al. *Design and synthesis of novel ACAT inhibitors: α,α -difluoroacetamide and α,α -difluoro- α -thioacetamide as surrogates of transition state analogs*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 068.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

263371

Lys³⁰-(N^ε-tetradecanoyl)-human glucagon-like peptide-2

ACTION – Derivative of human glucagon-like peptide-2 (hGLP-2) with a longer duration of action than parent peptides, claimed for use in the treatment of obesity or short-bowel syndrome.

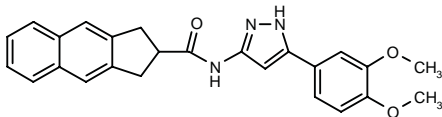
SOURCE – Novo Nordisk.

REFERENCES

1. Knudsen, L.B. et al. (Novo Nordisk A/S) *GLP-2 derivs*. WO 9808872.

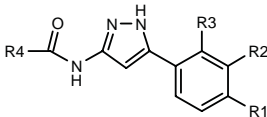
267947

N-[5-(3,4-Dimethoxyphenyl)-1H-pyrazol-3-yl]-2,3-dihydro-1H-cyclopenta[b]naphthalene-2-carboxamide



C25 H23 N3 O3; Mol wt: 413.4747

ACTION – Agent for the treatment of obesity, bulimia and diabetes with affinity for neuropeptide Y (NPY) Y₅ receptors, as demonstrated in a binding assay by an IC₅₀ value of 2.5 nM against [¹²⁵I]-PYY binding to Y₅ receptors expressed in clonal cells. Compound is also reported to inhibit bovine pancreatic polypeptide (bPP)-induced eating behavior in rats. Within this series of pyrazole derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
267948	Me	H	H	2-indanyl	C ₂₀ H ₁₉ N ₃ O
267949	H	Me	H	2-indanyl	C ₂₀ H ₁₉ N ₃ O
267950	H	H	Me	2-indanyl	C ₂₀ H ₁₉ N ₃ O
267951	Cl	H	H	1-indanyl	C ₁₉ H ₁₆ ClN ₃ O

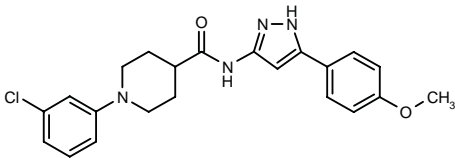
SOURCE – Banyu.

REFERENCES

1. Fukami, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Pyrazole derivs*. WO 9825907.

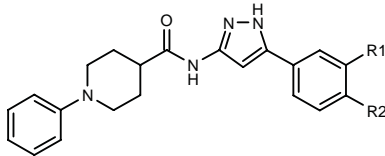
267952

1-(3-Chlorophenyl)-N-[5-(4-methoxyphenyl)1H-pyrazol-3-yl]piperidine-4-carboxamide



C22 H23 Cl N4 O2; Mol wt: 410.9027

ACTION – Agent for the treatment of obesity, bulimia and diabetes with affinity for neuropeptide Y (NPY) Y₅ receptors, as demonstrated in a binding assay by an IC₅₀ value of 39 nM against [¹²⁵I]-PYY binding to Y₅ receptors expressed in clonal cells. Compound is also reported to be effective at inhibiting NPY-induced eating behavior in rats. Within this series of aminopyrazole derivatives, the following are also included:



Compound	R1	R2	Formula
267953	H	Cl	C ₂₁ H ₂₁ ClN ₄ O
267954	H	OMe	C ₂₂ H ₂₄ N ₄ O ₂
267955	Cl	Cl	C ₂₁ H ₂₀ Cl ₂ N ₄ O

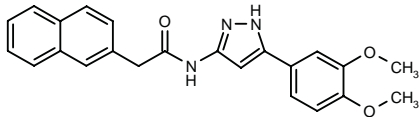
SOURCE – Banyu.

REFERENCES

1. Fukami, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel aminopyrazole derivs*. WO 9825908.

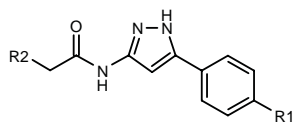
268361

N-[5-(3,4-Dimethoxyphenyl)-1H-pyrazol-3-yl]-2-(2-naphthyl)acetamide



C23 H21 N3 O3; Mol wt: 387.4369

ACTION – Agent for the treatment of obesity, bulimia or diabetes, a neuropeptide Y (NPY) Y₅ receptor antagonist with an IC₅₀ of 8.3 nM in a binding assay using [¹²⁵I]-PYY as the ligand and membranes from cells expressing the human receptor. It significantly inhibited increased food intake elicited by intracerebroventricular injection of bovine pancreatic polypeptide (bPP) in rats. Within this series of aminopyrazole derivatives, the following are also included:



Compound	R1	R2	Formula
268362	H	CH ₂ Ph	C ₁₈ H ₁₇ N ₃ O
268363	Cl	CH ₂ Ph	C ₁₈ H ₁₆ ClN ₃ O
268364	Cl	Ph	C ₁₇ H ₁₄ ClN ₃ O
268365	Cl	2-benzoxazolyl	C ₁₈ H ₁₃ ClN ₃ O ₂
268366	Cl	2-Naph	C ₂₁ H ₁₆ ClN ₃ O

SOURCE – Banyu.

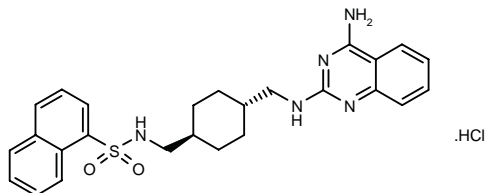
REFERENCES

1. Fukami, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Aminopyrazole derivs.* WO 9827063.

CGP-71683A

267576

trans-N-[4-(4-Amino-2-quinazolinylaminomethyl)cyclohexylmethyl]naphthalene-1-sulfonamide hydrochloride



C26 H29 N5 O2 S . HCl; Mol wt: 512.0750

ACTION – Potent and selective neuropeptide Y (NPY) Y₅ receptor antagonist, as demonstrated in binding studies using cloned human and rat Y₅ receptors (IC₅₀ = 2.89 ± 0.16 and 1.4 ± 0.09 nM, respectively) and cloned human Y₁, Y₂ and Y₄ subtypes (IC₅₀ = 8.37 ± 0.53, 1.89 ± 0.26 and 5.74 ± 0.23 μM, respectively), and in functional studies by inhibition of NPY-induced intracellular calcium transients in murine fibroblasts expressing the human Y₅ receptor (IC₅₀ = 5.8 ± 1.2 nM). It shows high lipophilicity and low water solubility and is being used as a lead in the development of Y₅ receptor antagonists with potential in the treatment of obesity.

SOURCE – Novartis.

REFERENCES

1. Rüeger, H. et al. (Novartis AG) *Receptor antagonists.* WO 9720823.
2. Hofbauer, K.G. *Role of NPY in the control of food intake.* Mod Manag Obes Non-Insulin Dependent Diabetes Mellitus (April 22-23, London) 1998.
3. Hofbauer, K.G. *Stimulation of food intake by neuropeptide Y: The possible role of the NPY Y5 receptor subtype.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst SD 6.5.
4. Rigollier, P. et al. *Synthesis and SAR of CGP 71683A, a potent and selective antagonist of the neuropeptide Y Y5 receptor.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.239.

ENP

263816

Seryl-alanyl-asparaginyl-seryl-asparaginyl-prolyl-alanyl-methionyl-alanyl-prolyl-arginyl-glutamyl-arginine

Enteric neural peptide

C55 H93 N21 O20 S; Mol wt: 1400.5330

ACTION – Intestinal peptide located in mammalian distal ileum, useful for regulating obesity, diabetes or eating disorders. Agonists are expected to be useful as satiety agents and/or for controlling fat intake, and antagonists may be used in conditions where appetite and fat intake are beneficially upregulated, such as in anorexia.

SOURCES – University of Washington, Seattle, WA (US); ZymoGenetics.

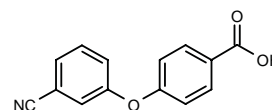
REFERENCES

1. Ensink, J.W. et al. (ZymoGenetics, Inc.; University of Washington) *Enteric neural peptide.* WO 9809991.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

267525

4-(3-Cyanophenoxy)benzoic acid



C14 H9 N O3; Mol wt: 239.2291

ACTION – Uricosuric agent from a series of substituted biaryl and biaryl ether derivatives whose activity was demonstrated by retention of phenol red in rats (ED₅₀ = 22.5 mg/kg p.o.), being more potent than benzbromarone (ED₅₀ = 58.8 mg/kg p.o.), as well as longer acting, its uricosuric effect lasting for about 18 h versus about 6 h for benzbromarone following oral doses of 50 mg/kg. It showed much less ulcerogenicity compared to benzbromarone (UD₅₀ > 400 mg/kg p.o. vs. 140 mg/kg p.o.). The compound was mainly excreted in the bile in rats and was not metabolized by human hepatic microsomes, suggesting that it may be useful in the treatment of hyperuricemic patients with impaired renal and hepatic function.

SOURCE – Kotobuki.

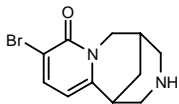
REFERENCES

1. Nimura, M. et al. *Synthesis and structure-activity relationships of substituted biaryl, biaryl ether derivatives as uricosuric agents.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 169.

TREATMENT OF POISONING
AND DRUG DEPENDENCY

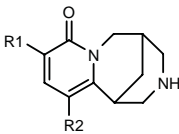
265125

9-Bromo-1,2,3,4,5,6-hexahydro-8*H*-1,5-methano-
pyrido[1,2-*a*][1,5]diazocin-8-one



C11 H13 Br N2 O; Mol wt: 269.1407

ACTION – Agent for the treatment of nicotine addiction, as well as for other neurological and psychiatric disorders related to reduced cholinergic function such as Huntington’s disease, tardive dyskinesia, schizophrenia, attention deficit hyperactivity disorder, various types of dementia, Parkinson’s disease, anxiety, etc., that acts as an antagonist at nicotinic acetylcholine receptors. Within this series of pyridone-fused azabicyclic compounds, the following are also specifically claimed:



Compound	R1	R2	Formula
267710	H	F	C ₁₁ H ₁₃ FN ₂ O
267711	Ph	H	C ₁₇ H ₁₈ N ₂ O
267712	NHCH2Ph	H	C ₁₈ H ₂₁ N ₃ O
267713	Ac	H	C ₁₃ H ₁₆ N ₂ O ₂
267714	2-Pyr	H	C ₁₆ H ₁₇ N ₃ O
267715	2,4-(F)2-Ph	H	C ₁₇ H ₁₆ F ₂ N ₂ O
267716	2-thiazolyl	H	C ₁₄ H ₁₅ N ₃ OS

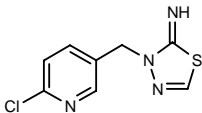
SOURCE – Pfizer.

REFERENCES

1. O'Neill, B.T. (Pfizer Inc.) *Pyridone-fused azabicyclic- or cytisine derivs., their preparation and their use in addiction therapy.* WO 9818798.

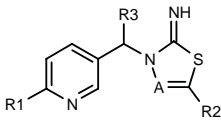
268655

3-(6-Chloropyridin-3-ylmethyl)-2,3-dihydro-1,3,4-
thiadiazol-2-imine

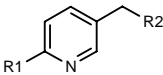


C8 H7 Cl N4 S; Mol wt: 226.6903

ACTION – Agent for the treatment of addiction to substances such as tobacco, as well as neurological and psychiatric disorders such as Alzheimer’s disease, Parkinson’s disease, attention deficit hyperactivity disorder, anxiety, obesity, Tourette’s syndrome and ulcerative colitis, with affinity for nicotinic acetylcholine receptors. Within this series of specifically claimed heterocyclylmethylpyridine derivatives, the following are also included:



Compound	R1	R2	R3	A	Formula
268656	H	Me	H	CH	C ₁₀ H ₁₁ N ₃ S
268657	Cl	Me	H	N	C ₉ H ₉ ClN ₄ S
268660	H	H	H	N	C ₈ H ₈ N ₄ S
268661	Cl	H	Me	CH	C ₁₀ H ₁₀ ClN ₃ S
268662	Cl	H	Me	N	C ₉ H ₉ ClN ₄ S
268667	H	Me	H	N	C ₉ H ₁₀ N ₄ S



Compound	R1	R2	Formula
268658	Cl	6-Cl-3-imino-2,3-dihydro-2-pyridazinyl	C ₁₀ H ₈ Cl ₂ N ₄
268659	Cl	2-imino-2,3-dihydro-3-benzothiazolyl	C ₁₃ H ₁₀ ClN ₃ S
268663	Cl	2-imino-3-thiazolidinyl	C ₉ H ₁₀ ClN ₃ S
268664	H	2-imino-3-thiazolidinyl	C ₉ H ₁₁ N ₃ S
268665	H	2-imino-5,7-(Me)2- -2,3-dihydro-1,8-naphthyridin-1-yl	C ₁₆ H ₁₈ N ₄
268666	H	6-Cl-3-imino-2,3-dihydro-2-pyridazinyl	C ₁₀ H ₉ ClN ₄

SOURCE – Pfizer.

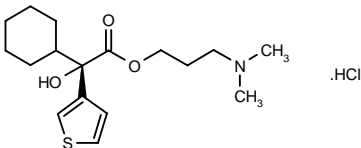
REFERENCES

1. Dorff, P.H. et al. (Pfizer Inc.) *(N-(Pyridinylmethyl)-heterocyclic)ylideneamine cpds. as nicotinic acetylcholine receptor binding agents.* EP 857725, JP 98226684.

CEB-1957

267969

2(*S*)-Cyclohexyl-2-hydroxy-2-(3-thienyl)acetic acid 3-
(dimethylamino)propyl ester hydrochloride



C17 H27 N O3 S . HCl; Mol wt: 361.9312

M.p. 199-200 °C; [α]_D²⁵ –11.27° (c 1.0, MeOH).

ACTION – Potent anticholinergic agent with a different muscarinic receptor subtype affinity profile in rat brain compared to atropine; it displayed very high affinity for the high-affinity site on the M₃ receptor (K_i = 0.12-0.77 nM) and for the high-affinity site on the M₂ receptor in frontal cortex and striatum (K_i = 0.26-0.60 nM), with lower affinity for low-affinity sites on these receptors (K_i = 55-1110 nM) and for M₁ receptors (K_i = 13.2-46.7 nM). It was more potent than atropine in reducing mortality and symptoms in rats treated with sarin at 2 x LD₅₀ (ED₅₀ = 1.9 mg/kg i.m. vs. 19.6 mg/kg i.m.). Potentially useful as an alternative to atropine in organophosphorus poisoning.

SOURCE – Centre d'Etudes du Bouchet, Vert-le-Petit (FR).

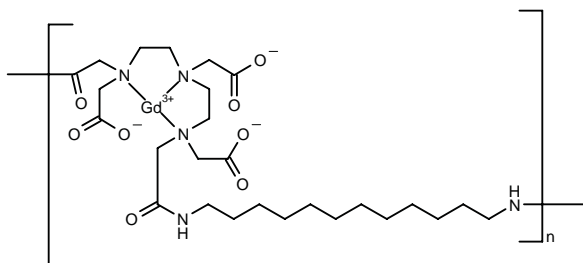
REFERENCES

1. Bizot, J.-C. *Effects of various drugs including organophosphorus compounds (OPC) and therapeutic compounds against OPC on DRL responding*. Pharmacol Biochem Behav 1998, 59(4): 1069.
2. Lienne, M. et al. *Direct enantiomeric separation of anticholinergic drugs derived from (±)-cyclohexyl (2-thienyl)glycolic acid on a novel alpha1-acid glycoprotein-bonded chiral stationary phase (chiral-AGP)*. J Chromatogr 1989, 467(2): 406.
3. Trovero, F. et al. *Pharmacological profile of CEB-1957 and atropine toward brain muscarinic receptors and comparative study of their efficacy against sarin poisoning*. Toxicol Appl Pharmacol 1998, 150(2): 321.

DIAGNOSTIC AGENTS

267530

Polymeric gadolinium complex



(C26 H44 Gd N5 O8)_n

ACTION – Contrast agent for use in magnetic resonance imaging (MRI), a metallated polymeric polychelant with high relaxivity.

SOURCE – Nycomed Imaging.

REFERENCES

1. Hollister, K.R. et al. (Nycomed Imaging AS) *Polymeric contrast agents for medical imaging*. US 5801228.

E25a

263818

263-Amino-acid protein with a molecular weight of approximately 40 kD

ACTION – Cell-surface human protein that is upregulated in cancerous cells, claimed for use as a diagnostic marker for cancer, and more particularly, as a specific therapeutic target for hormone-refractory prostate cancer.

SOURCE – University of California, Oakland, CA (US).

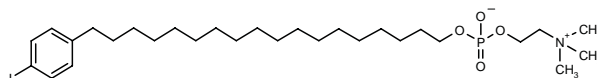
REFERENCES

1. University of California, Oakland. *E25a protein, methods for production and use thereof*. WO 9810069.

NM-404

267572

2-[Hydroxy[18-(4-iodophenyl)octadecyloxy]phosphinyloxy]-N,N,N-trimethylethanaminium inner salt



C29 H53 I N O4 P; Mol wt: 637.6147

ACTION – Radiolabeled tumor imaging agent from a series of phospholipid ether analogs, with a longer plasma half-life, better tumor/liver and tumor/kidney ratios, and significantly superior imaging properties compared to the prototype NM-324 in SCID mice bearing human lung adenocarcinoma A549 and human prostate cancer PC-3 tumors. Selected for clinical studies in cancer patients.

SOURCE – University of Michigan, Ann Arbor, MI (US).

REFERENCES

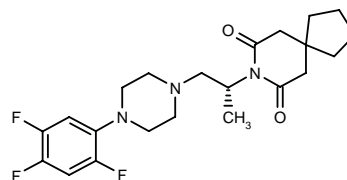
1. Counsell, R.E. et al. (University of Michigan) *Radiolabeled phospholipid ether analogs and methods of using the same*. WO 9824480.
2. Counsell, R.E. et al. *Synthesis and tumor imaging properties of a homologous series of radiolabeled arylalkylphosphatidyl cholines*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.257.

PHARMACOLOGICAL TOOLS

SNAP-8719

267069

8-[1(R)-Methyl-2-[4-(2,4,5-trifluorophenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione



C22 H28 F3 N3 O2; Mol wt: 423.4762

ACTION – Potent and selective α_{1D} -adrenoceptor antagonist ($K_i = 1.3$ nM) with 95-fold selectivity over dopamine D_3 receptors and > 100-fold selectivity over other α_1 -adrenoceptor subtypes, 5-HT_{1A} and dopamine D_2 receptors in binding studies using cloned human receptors. In functional studies, it also showed high potency and selectivity as an α_{1D} -adrenoceptor antagonist, giving K_i values for inhibition of phenylephrine-induced contractions in rat thoracic aorta (α_{1D}), rat epididymal vas deferens (α_{1A}) and rat spleen (α_{1B}) of 3.3, 6760 and 209 nM, respectively. Potentially useful as a tool for studying the physiological roles of α_1 -adrenoceptor subtypes.

SOURCE – Synaptic.

REFERENCES

1. Konkel, M.J. et al. *Discovery of antagonists selective for the α_{1D} -adrenoceptor*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 129.

SOURCE – Centre d'Etudes du Bouchet, Vert-le-Petit (FR).

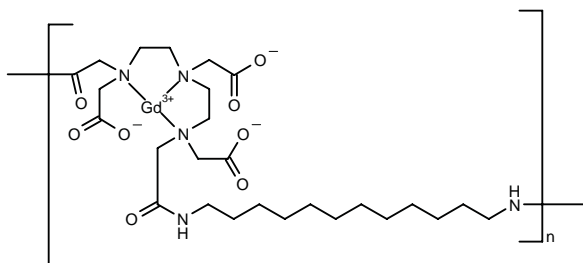
REFERENCES

1. Bizot, J.-C. *Effects of various drugs including organophosphorus compounds (OPC) and therapeutic compounds against OPC on DRL responding*. Pharmacol Biochem Behav 1998, 59(4): 1069.
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263-Amino-acid protein with a molecular weight of approximately 40 kD

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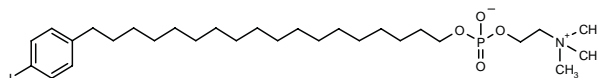
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NM-404

267572

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SOURCE – University of Michigan, Ann Arbor, MI (US).

REFERENCES

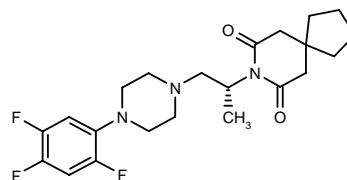
1. Counsell, R.E. et al. (University of Michigan) *Radiolabeled phospholipid ether analogs and methods of using the same*. WO 9824480.
2. Counsell, R.E. et al. *Synthesis and tumor imaging properties of a homologous series of radiolabeled arylalkylphosphatidyl cholines*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.257.

PHARMACOLOGICAL TOOLS

SNAP-8719

267069

8-[1(R)-Methyl-2-[4-(2,4,5-trifluorophenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione



C22 H28 F3 N3 O2; Mol wt: 423.4762

ACTION – Potent and selective α_{1D} -adrenoceptor antagonist ($K_i = 1.3$ nM) with 95-fold selectivity over dopamine D_3 receptors and > 100-fold selectivity over other α_1 -adrenoceptor subtypes, 5-HT_{1A} and dopamine D_2 receptors in binding studies using cloned human receptors. In functional studies, it also showed high potency and selectivity as an α_{1D} -adrenoceptor antagonist, giving K_i values for inhibition of phenylephrine-induced contractions in rat thoracic aorta (α_{1D}), rat epididymal vas deferens (α_{1A}) and rat spleen (α_{1B}) of 3.3, 6760 and 209 nM, respectively. Potentially useful as a tool for studying the physiological roles of α_1 -adrenoceptor subtypes.

SOURCE – Synaptic.

REFERENCES

1. Konkel, M.J. et al. *Discovery of antagonists selective for the α_{1D} -adrenoceptor*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 129.

SOURCE – Centre d'Etudes du Bouchet, Vert-le-Petit (FR).

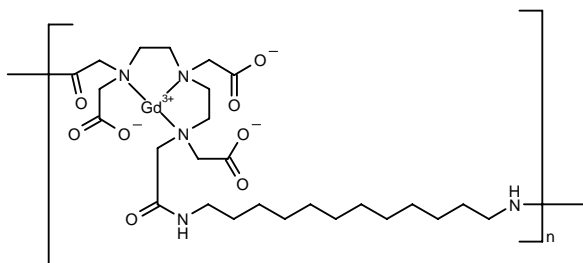
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1. Bizot, J.-C. *Effects of various drugs including organophosphorus compounds (OPC) and therapeutic compounds against OPC on DRL responding*. Pharmacol Biochem Behav 1998, 59(4): 1069.
2. Lienne, M. et al. *Direct enantiomeric separation of anticholinergic drugs derived from (±)-cyclohexyl (2-thienyl)glycolic acid on a novel alpha1-acid glycoprotein-bonded chiral stationary phase (chiral-AGP)*. J Chromatogr 1989, 467(2): 406.
3. Trovero, F. et al. *Pharmacological profile of CEB-1957 and atropine toward brain muscarinic receptors and comparative study of their efficacy against sarin poisoning*. Toxicol Appl Pharmacol 1998, 150(2): 321.

DIAGNOSTIC AGENTS

267530

Polymeric gadolinium complex



(C₂₆ H₄₄ Gd N₅ O₈)_n

ACTION – Contrast agent for use in magnetic resonance imaging (MRI), a metallated polymeric polychelant with high relaxivity.

SOURCE – Nycomed Imaging.

REFERENCES

1. Hollister, K.R. et al. (Nycomed Imaging AS) *Polymeric contrast agents for medical imaging*. US 5801228.

E25a

263818

263-Amino-acid protein with a molecular weight of approximately 40 kD

ACTION – Cell-surface human protein that is upregulated in cancerous cells, claimed for use as a diagnostic marker for cancer, and more particularly, as a specific therapeutic target for hormone-refractory prostate cancer.

SOURCE – University of California, Oakland, CA (US).

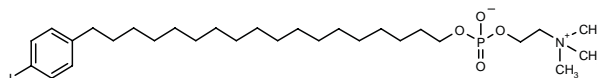
REFERENCES

1. University of California, Oakland. *E25a protein, methods for production and use thereof*. WO 9810069.

NM-404

267572

2-[Hydroxy[18-(4-iodophenyl)octadecyloxy]phosphinyloxy]-N,N,N-trimethylethanaminium inner salt



C₂₉ H₅₃ I N O₄ P; Mol wt: 637.6147

ACTION – Radiolabeled tumor imaging agent from a series of phospholipid ether analogs, with a longer plasma half-life, better tumor/liver and tumor/kidney ratios, and significantly superior imaging properties compared to the prototype NM-324 in SCID mice bearing human lung adenocarcinoma A549 and human prostate cancer PC-3 tumors. Selected for clinical studies in cancer patients.

SOURCE – University of Michigan, Ann Arbor, MI (US).

REFERENCES

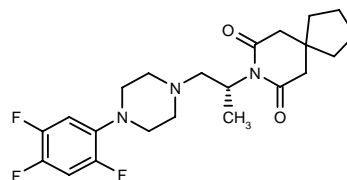
1. Counsell, R.E. et al. (University of Michigan) *Radiolabeled phospholipid ether analogs and methods of using the same*. WO 9824480.
2. Counsell, R.E. et al. *Synthesis and tumor imaging properties of a homologous series of radiolabeled arylalkylphosphatidyl cholines*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.257.

PHARMACOLOGICAL TOOLS

SNAP-8719

267069

8-[1(R)-Methyl-2-[4-(2,4,5-trifluorophenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione



C₂₂ H₂₈ F₃ N₃ O₂; Mol wt: 423.4762

ACTION – Potent and selective α_{1D} -adrenoceptor antagonist ($K_i = 1.3$ nM) with 95-fold selectivity over dopamine D₃ receptors and > 100-fold selectivity over other α_1 -adrenoceptor subtypes, 5-HT_{1A} and dopamine D₂ receptors in binding studies using cloned human receptors. In functional studies, it also showed high potency and selectivity as an α_{1D} -adrenoceptor antagonist, giving K_i values for inhibition of phenylephrine-induced contractions in rat thoracic aorta (α_{1D}), rat epididymal vas deferens (α_{1A}) and rat spleen (α_{1B}) of 3.3, 6760 and 209 nM, respectively. Potentially useful as a tool for studying the physiological roles of α_1 -adrenoceptor subtypes.

SOURCE – Synaptic.

REFERENCES

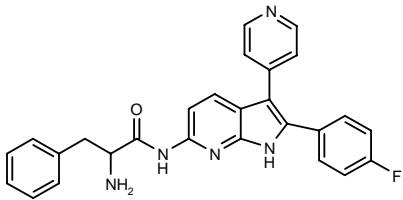
1. Konkel, M.J. et al. *Discovery of antagonists selective for the α_{1D} -adrenoceptor*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 129.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

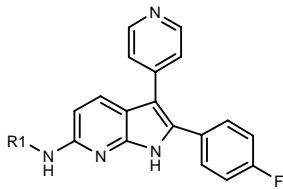
265521

D,L-Phenylalanine 2-(4-fluorophenyl)-3-(4-pyridyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-ylamide



C27 H22 F N5 O; Mol wt: 451.5028

ACTION – An inhibitor of proinflammatory cytokines such as tumor necrosis factor (TNF- α), IL-1 β , IL-6 and IL-8, as well as cyclooxygenase, with potential in the treatment or prevention of pain and diabetes. Other specifically claimed compounds from this series of fused pyrrole derivatives include the following:



Compound	R1	Formula
266519	SO2Me	C ₁₉ H ₁₅ FN ₄ O ₂ S
266520	CO(CH ₂) ₅ NH ₂	C ₂₄ H ₂₄ FN ₅ O
266521	Me-L-Ala-	C ₂₂ H ₂₀ FN ₅ O

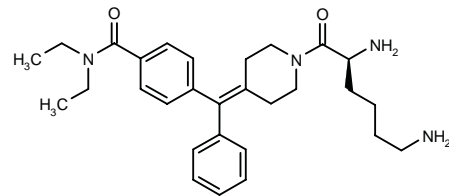
SOURCE – Amgen.

REFERENCES

1. Zablocki, J.A. et al. (Amgen Inc.) *Aryl and heteroaryl substd. fused pyrrole antiinflammatory agents*. WO 9822457.

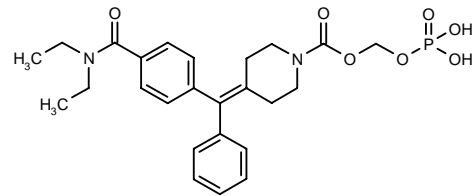
268896

N,N-Diethyl-4-[1-[1-(*L*-lysyl)piperidin-4-ylidene]-1-phenylmethyl]benzamide



C29 H40 N4 O2; Mol wt: 476.6610

ACTION – Analgesic agent with high affinity and selectivity for δ -opioid receptors, also reported to be useful as an immunomodulator. Another representative compound within this series of specifically claimed piperidine derivatives is:



268897: C25 H31 N2 O7 P

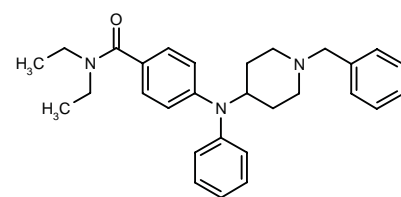
SOURCE – Astra.

REFERENCES

1. Delorme, D. et al. (Astra AB;Astra Pharma Inc.) *Novel cpds. with analgesic effect*. WO 9828275.

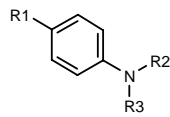
268898

4-[*N*-(1-Benzylpiperidin-4-yl)-*N*-phenylamino]-*N,N*-diethylbenzamide

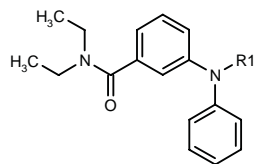


C29 H35 N3 O; Mol wt: 441.6155

ACTION – Analgesic agent with high affinity and selectivity for δ -opioid receptors, also reported to be useful as an immunomodulator. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
268899	CON(Et)2	1-(PhCH2)-4-Pip	4-Me-Ph	C ₃₀ H ₃₇ N ₃ O
268900	CON(Et)2	1-(PhCH2)-4-Pip	1-Naph	C ₃₃ H ₃₇ N ₃ O
268901	CON(Et)2	1-(PhCH2)-4-Pip	2-Naph	C ₃₃ H ₃₇ N ₃ O
268902	CON(Et)2	4-Pip	Ph	C ₂₂ H ₂₉ N ₃ O
268903	CON(Et)2	4-Pip	1-Naph	C ₂₆ H ₃₁ N ₃ O
268904	CON(Et)2	4-Pip	2-Naph	C ₂₆ H ₃₁ N ₃ O
268905	CON(Et)2	3-Pip	Ph	C ₂₂ H ₂₉ N ₃ O
268907	CON(Et)2	1-(PhCH2CH2)-4-Pip	Ph	C ₃₀ H ₃₇ N ₃ O
268909	CON(Et)2	1-(PhCH2)-3-Pip	Ph	C ₂₉ H ₃₅ N ₃ O
268912	CON(Et)2	1-(PhCH2)- -3-pyrrolidinyl	Ph	C ₂₈ H ₃₃ N ₃ O
268913	CON(Et)2	3-pyrrolidinyl	Ph	C ₂₁ H ₂₇ N ₃ O
268914	SO2N(Et)2	1-(PhCH2)-4-Pip	Ph	C ₂₈ H ₃₅ N ₃ O ₂ S
268915	SO2N(Et)2	4-Pip	Ph	C ₂₁ H ₂₉ N ₃ O ₂ S



Compound	R1	Formula
268906	1-(PhCH2)-4-Pip	C ₂₉ H ₃₅ N ₃ O
268908	4-Pip	C ₂₂ H ₂₉ N ₃ O
268910	1-(PhCH2)-3-Pip	C ₂₉ H ₃₅ N ₃ O
268911	3-Pip	C ₂₂ H ₂₉ N ₃ O

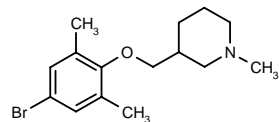
SOURCE – Astra.

REFERENCES

1. Pelcman, B. and Roberts, E. (Astra AB;Astra Pharma Inc.) *Novel cpds. with analgesic effect.* WO 9828270.

268996

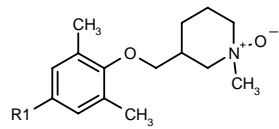
3-(4-Bromo-2,6-dimethylphenoxy)methyl-1-methyl-piperidine



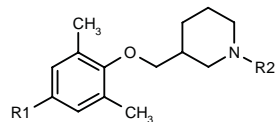
C15 H22 Br N O; Mol wt: 312.2488

ACTION– Agent for the treatment of neuropathic pain that acts by virtue of its use-dependent sodium channel-blocking activity, as demonstrated *in vitro* by blockade of high-frequency nerve activity in rat vagus nerve. *In vivo* activity was demonstrated in the mechanical allodynia assay in rats, where pain is produced by spinal nerve ligation, and in the cold allodynia assay in rats, where pain is produced by unilateral mononeuropathy, following p.o. administration. In addition, compound was reported to be

active in the mechanical hyperalgesia and thermal hyperalgesia assays in rats. Within this series of phenoxyethylpiperidine derivatives, the following are also specifically claimed:



Compound	R1	Formula
268997	Br	C ₁₅ H ₂₂ BrNO ₂
269002	H	C ₁₅ H ₂₃ NO ₂



Compound	R1	R2	Isomer	Formula
268998	Br	Me	S	C ₁₅ H ₂₂ BrNO
268999	Br	H		C ₁₄ H ₂₀ BrNO
269000	Br	H	S	C ₁₄ H ₂₀ BrNO
269001	H	Me		C ₁₅ H ₂₃ NO
269003	H	Me	S	C ₁₅ H ₂₃ NO

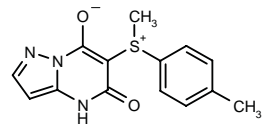
SOURCE – Roche.

REFERENCES

1. Flippin, L.A. et al. (F. Hoffmann-La Roche AG) *Phenoxyethyl piperidine derivs. being sodium channel blockers.* EP 869119, JP 98287649.

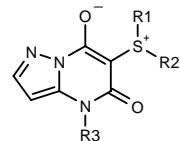
269305

S-Methyl-S-(4-methylphenyl)-S-(7-oxido-5-oxo-4,5-dihydropyrazolo[1,5-a]pyrimidin-6-yl)sulfonium



C14 H13 N3 O2 S; Mol wt: 287.3417

ACTION – Analgesic and antiinflammatory agent, also reported to possess sedative, antibacterial, antiviral, hypoglycemic, hypolipidemic, antihypertensive and carcinostatic activity. Within this series of pyrazolo-[1,5-a]pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269306	2-(AcNH)-Ph	Me	H	C ₁₅ H ₁₄ N ₄ O ₃ S
269307	CH2CO2Me	Me	H	C ₁₀ H ₁₁ N ₃ O ₄ S
269308	Ph	CH2- CH2OH	H	C ₁₄ H ₁₃ N ₃ O ₃ S
269309	-CH2CH2SCH2CH2-		H	C ₁₀ H ₁₁ N ₃ O ₂ S ₂
269310	-CH2CH2N(COPh)CH2CH2-		H	C ₁₇ H ₁₆ N ₄ O ₃ S
269311	Pr	Me	H	C ₁₀ H ₁₃ N ₃ O ₂ S
269312	Pr	Me	4-MeO-Ph- CH2	C ₁₈ H ₂₁ N ₃ O ₃ S

SOURCE – Otsuka.

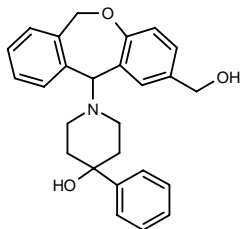
REFERENCES

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KF-24705*

250764

1-[2-(Hydroxymethyl)-6,11-dihydrodibenzo[*b,e*]oxepin-11-yl]-4-phenylpiperidin-4-ol



C26 H27 N O3; Mol wt: 401.5033

ACTION – Analgesic agent from a series of 4-phenylpiperidine derivatives, proven active in the acetic acid-induced writhing test in mice (ED₅₀ = 0.98 mg/kg s.c., 1.31 mg/kg p.o.).

SOURCE – Kyowa Hakko.

REFERENCES

1. Kumazawa, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Phenylpiperidine derivs.* WO 9710213.

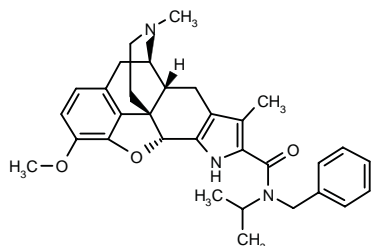
2. Kumazawa, T. et al. *Synthesis and analgesic activity of 4-phenylpiperidine derivatives.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.287.

*Identified compound **250764** (see **250052**) Drug Data Report 1997, 019(07): 0589.

SB-237596^{2,4}

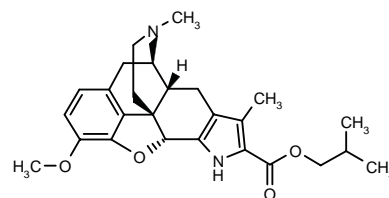
267504

N-Benzyl-4,5 α -epoxy-*N*-isopropyl-3-methoxy-4',17-dimethyl-6,7-didehydropyrrolo[2',3':6,7]morphinan-5'-carboxamide



C32 H37 N3 O3; Mol wt: 511.6623

ACTION – Analgesic agent, a potent and selective δ -opioid receptor agonist (K_i = 1.1 nM; μ/δ = 178; κ/δ > 1000), expected to be free of adverse effects associated with μ - and κ -opioid receptor interactions. Another related pyrrolomorphinan is:



SB-235863¹⁻⁵ [267505]: C26 H32 N2 O4

SOURCE – SmithKline Beecham.

REFERENCES

1. Dondio, G. and Ronzoni, S. (SmithKline Beecham plc) *Heterocycle-condensed morphinoid derivs.* EP 770081, JP 98502657, WO 9602545.

2. Dondio, G. et al. (SmithKline Beecham SpA) *Heterocycle-condensed morphinoid derivs. (II).* EP 880526, WO 9725331.

3. Bingham, S. et al. *The δ agonist, SB-235863A reverses thermal hyperalgesia in a rat model of established neuropathic pain.* Soc Neurosci Abst 1998, 24(Part 1): Abst 352.15.

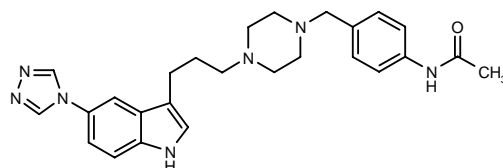
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5. Pozzi, O. et al. *SB 235863, a new non peptidic δ opioid receptor agonist with antihyperalgesic activity.* Soc Neurosci Abst 1998, 24(Part 1): Abst 352.16.

ANTIMIGRAINE DRUGS

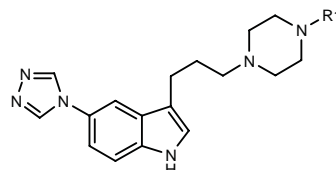
268783

N-[4-[4-[3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl]-piperazin-1-ylmethyl]phenyl]acetamide

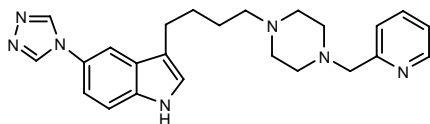


C26 H31 N7 O; Mol wt: 457.5789

ACTION – Antimigraine agent, a 5-HT_{1D} receptor agonist with at least 10-fold selectivity for the human 5-HT_{1D} receptor subtype relative to the 5-HT_{1B} subtype and thus expected to be associated with fewer side effects, notably adverse cardiovascular effects, than non-subtype-selective 5-HT_{1D} receptor agonists. Within this series of specifically claimed piperazine, piperidine and tetrahydropyridine derivatives, the following are also included:



Compound	R1	Formula
268785	4-(NH ₂ CONH)-PhCH ₂ CH ₂	C ₂₆ H ₃₂ N ₈ O
268786	4-(NH ₂ SO ₂)-PhCH ₂	C ₂₄ H ₂₉ N ₇ O ₂ S
268787	2-(2-Me-5-tetrazolyl)-PhCH ₂	C ₂₆ H ₃₀ N ₁₀
268788	CH(Ph)CONH ₂	C ₂₅ H ₂₉ N ₇ O
268789	CH(Ph)CH ₂ N(Me)CO ₂ Me	C ₂₈ H ₃₅ N ₇ O ₂



268784: C₂₄ H₂₉ N₇

SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Piperazine, piperidine and tetrahydropyridine deriv. of indol-3-alkyl as 5-HT_{1D}-alpha agonists*. US 5807857, WO 9532196.

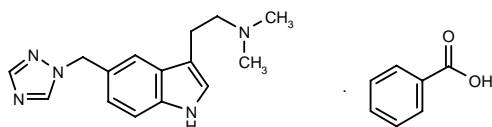
RIZATRIPTAN BENZOATE

216363

3-[2-(Dimethylamino)ethyl]-5-(1,2,4-triazol-1-ylmethyl)-indole benzoate

MK-0462⁺

MK-462



C₁₅ H₁₉ N₅ . C₇ H₆ O₂; Mol wt: 391.4725

ACTION – Antimigraine agent, a potent and selective 5-HT_{1B/1D} receptor agonist.

INDICATION – Acute treatment of migraine attacks with or without aura.

PRESENTATION – Tablets and wafers (orally disintegrating tablets), 7.265 and 14.530 mg (equivalent to 5 and 10 mg free base, respectively).

PROPRIETARY NAME – Maxalt (GB, MX, NL, UK, US).

SOURCE – Merck & Co.

RECENT REFERENCES

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- Beer, M. et al. *An in vitro pharmacological profile of rizatriptan*. Cephalalgia 1997, 17(3): 390.
- Block, G.A. et al. *Efficacy and safety of rizatriptan versus standard care during long-term treatment for migraine*. 12th Migraine Trust Int Symp (Sept 1-4, London) 1998, Abst P.51.
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- Cumberbatch, M.J. et al. *Rizatriptan has central antinociceptive effects against durally evoked responses*. Eur J Pharmacol 1997, 328(1): 37.
- Cumberbatch, M.J. et al. *Rizatriptan inhibits trigeminal nociceptive responses in an electrophysiological assay in the anaesthetized rat*. Br J Pharmacol 1997, 120(Suppl.): Abst 213P.
- Gijsman, H. et al. *Double-blind, placebo-controlled, dose-finding study of rizatriptan (MK-462) in the acute treatment of migraine*. Cephalalgia 1997, 17(6): 647.
- Goldberg, M.R. et al. *Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine*. Clin Pharmacol Ther 1998, 63(2): Abst PII-54.
- Goldberg, M.R. et al. *Pharmacokinetics of rizatriptan in patients with mild-moderate hepatic insufficiency*. Clin Pharmacol Ther 1998, 63(2): Abst PII-55.

10. Hester Visser, W. *Clinical review of rizatriptan*. 2nd Int Conf Migraine (April 6-7, Philadelphia) 1998.

11. Kramer, M.S. et al. *A placebo-controlled crossover study of rizatriptan in the treatment of multiple migraine attacks*. Neurology 1998, 51(3): 773.

12. Kramer, M.S. et al. *Placebo-controlled, double-blind study of rizatriptan in multiple attacks of acute migraine*. 49th Annu Meet Amer Acad Neurol (April 12-19, Boston) 1997, Abst P01.136.

13. Lee, Y. et al. *Pharmacokinetics (PK) of oral rizatriptan[®] in healthy males and females*. Clin Pharmacol Ther 1998, 63(2): Abst PI-23.

14. Longmore, J. et al. *Rizatriptan selectively contracts human middle meningeal over coronary artery: Comparison with sumatriptan*. Cephalalgia 1997, 17(3): 388.

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16. Norman, B.A. et al. *Two-period crossover comparison of rizatriptan 5 mg and 10 mg to sumatriptan 25 mg and 50 mg for the acute treatment of migraine*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S46.005.

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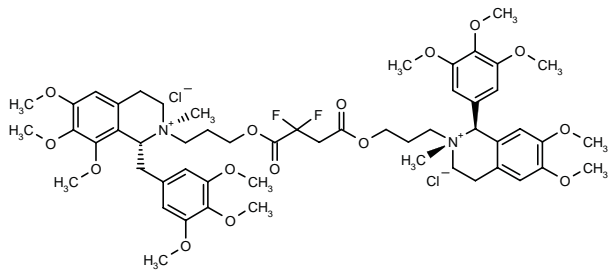
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ADJUNCTS TO ANESTHESIA

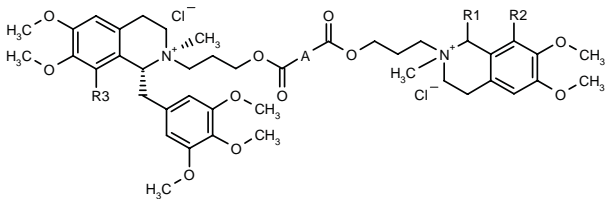
269719

2,2-Difluorosuccinic acid 4-[3-[6,7-dimethoxy-2(*R*)-methyl-1(*S*)-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl] 1-[3-[6,7,8-trimethoxy-2(*S*)-methyl-1(*R*)-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl] diester dichloride



C54 H72 Cl2 F2 N2 O15 ; Mol wt: 1098.0640

ACTION – Ultra-short-acting, nondepolarizing neuromuscular blocking agent for use as a skeletal muscle relaxant during emergency intubation procedures, routine surgery and in postoperative settings. When tested *in vivo* in anesthetized rhesus monkeys, it blocked the twitch response following stimulation of the common peroneal nerve with an ED₉₅ value of 0.035 mg/kg i.v. and a duration of action of 9.5 min; histamine release was observed only at much higher concentrations (3.2 mg/kg i.v.). Other compounds from this series of substituted isoquinolines include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
269756	3,4,5-(MeO)3-PhCH2	H	H	-C(Cl)=CH-	1R,2S	C ₅₄ H ₇₁ Cl ₃ N ₂ O ₁₄
269757	3,4,5-(MeO)3-Ph	H	H	-(CH2)6-	1S,2R	C ₅₇ H ₈₀ Cl ₂ N ₂ O ₁₄
269760	3,4,5-(MeO)3-Ph	H	H	(Z)-C(Cl)=CH-	1S,2R	C ₅₃ H ₆₉ Cl ₃ N ₂ O ₁₄
269761	3,4,5-(MeO)3-Ph	H	H	(E)-CH=CH-	1R,2S	C ₅₃ H ₇₀ Cl ₂ N ₂ O ₁₄
269762	4-MeO-Ph	H	H	(Z)-C(Cl)=CH-	1S,2S	C ₅₁ H ₆₅ Cl ₃ N ₂ O ₁₂
269763	3,4-(MeO)2-Ph	H	H	(Z)-C(Cl)=CH-	1S,2R	C ₅₂ H ₆₇ Cl ₃ N ₂ O ₁₃
269764	3,4-(F)2-Ph	H	H	(Z)-C(Cl)=CH-	1S,2R	C ₅₀ H ₆₁ Cl ₃ F ₂ N ₂ O ₁₁
269765	3,4,5-(MeO)3-Ph	H	H	-C(F2)CH2-	1S,2R	C ₅₃ H ₇₀ Cl ₂ F ₂ N ₂ O ₁₄
269766	3,4-(MeO)2-Ph	OMe	H	-C(F2)CH2-	1S,2R	C ₅₃ H ₇₀ Cl ₂ F ₂ N ₂ O ₁₄
269767	3,4-(MeO)2-Ph	H	H	-C(F2)CH2-	1S,2R	C ₅₂ H ₆₈ Cl ₂ F ₂ N ₂ O ₁₃
269768	3,4,5-(MeO)3-Ph	H	H	-CH(F)CH2-	1S,2S	C ₅₃ H ₇₁ Cl ₂ FN ₂ O ₁₄
269769	3,4-(MeO)2-Ph	H	H	-C(F2)CH2-	1R,2S	C ₅₂ H ₆₈ Cl ₂ F ₂ N ₂ O ₁₃
269770	3,4,5-(MeO)3-Ph	H	OMe	(Z)-C(F)=CH-	1S,2R	C ₅₄ H ₇₁ Cl ₂ FN ₂ O ₁₅

SOURCES – Cornell Research Foundation, Ithaca, NY (US); Glaxo Wellcome.

REFERENCES

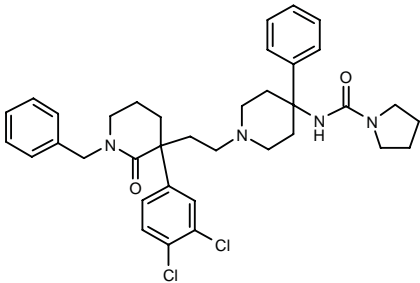
1. Bigham, E.C. et al. (Glaxo Wellcome plc;Cornell Research Foundation, Inc.) *Subst. isoquinolines as ultra short acting neuromuscular blockers*. WO 9842674, WO 9842675.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

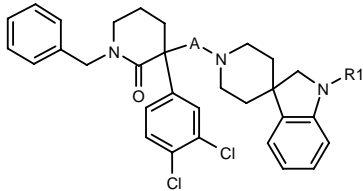
265101

N-[1-[2-[1-Benzyl-3-(3,4-dichlorophenyl)-2-oxopiperidin-3-yl]ethyl]-4-phenylpiperidin-4-yl]pyrrolidine-1-carboxamide



C36 H42 Cl2 N4 O2; Mol wt: 633.6598

ACTION – Potent and selective human neurokinin NK₃ receptor antagonist with a K_i value < 5 nM against [¹²⁵I]-His[MePhe⁷]-NKB binding to human cloned NK₃ receptors. Potentially useful in the treatment of conditions such as anxiety, asthma, depression, epilepsy, Parkinson's disease, schizophrenia, migraine and pain. A representative compound from a series of cyclic amide derivatives, wherein the following are also specifically claimed:

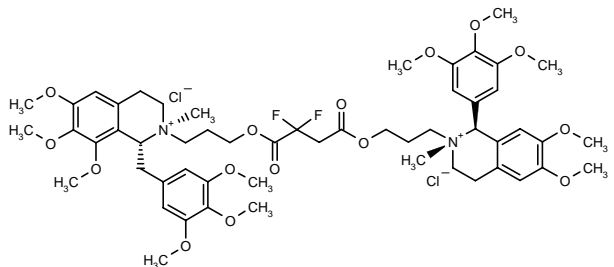


Compound	R1	A	Formula
267664	1-pyrrolidinyl-CO	-(CH2)2-	C ₃₇ H ₄₂ Cl ₂ N ₄ O ₂
267665	SO2Me	-(CH2)2-	C ₃₃ H ₃₇ Cl ₂ N ₃ O ₃ S
267668	SO2Me	-(CH2)3-	C ₃₄ H ₃₉ Cl ₂ N ₃ O ₃ S

ADJUNCTS TO ANESTHESIA

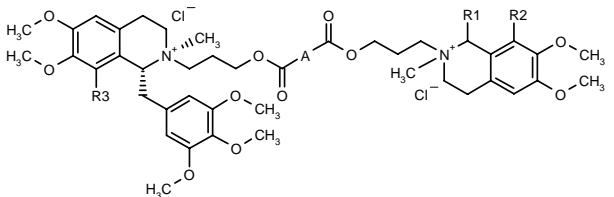
269719

2,2-Difluorosuccinic acid 4-[3-[6,7-dimethoxy-2(*R*)-methyl-1(*S*)-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl] 1-[3-[6,7,8-trimethoxy-2(*S*)-methyl-1(*R*)-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl] diester dichloride



C54 H72 Cl2 F2 N2 O15 ; Mol wt: 1098.0640

ACTION – Ultra-short-acting, nondepolarizing neuromuscular blocking agent for use as a skeletal muscle relaxant during emergency intubation procedures, routine surgery and in postoperative settings. When tested *in vivo* in anesthetized rhesus monkeys, it blocked the twitch response following stimulation of the common peroneal nerve with an ED₉₅ value of 0.035 mg/kg i.v. and a duration of action of 9.5 min; histamine release was observed only at much higher concentrations (3.2 mg/kg i.v.). Other compounds from this series of substituted isoquinolines include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
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269757	3,4,5-(MeO)3-Ph	H	H	-(CH2)6-	1S,2R	C ₅₇ H ₈₀ Cl ₂ N ₂ O ₁₄
269760	3,4,5-(MeO)3-Ph	H	H	(Z)-C(Cl)=CH-	1S,2R	C ₅₃ H ₆₉ Cl ₃ N ₂ O ₁₄
269761	3,4,5-(MeO)3-Ph	H	H	(E)-CH=CH-	1R,2S	C ₅₃ H ₇₀ Cl ₂ N ₂ O ₁₄
269762	4-MeO-Ph	H	H	(Z)-C(Cl)=CH-	1S,2S	C ₅₁ H ₆₅ Cl ₃ N ₂ O ₁₂
269763	3,4-(MeO)2-Ph	H	H	(Z)-C(Cl)=CH-	1S,2R	C ₅₂ H ₆₇ Cl ₃ N ₂ O ₁₃
269764	3,4-(F)2-Ph	H	H	(Z)-C(Cl)=CH-	1S,2R	C ₅₀ H ₆₁ Cl ₃ F ₂ N ₂ O ₁₁
269765	3,4,5-(MeO)3-Ph	H	H	-C(F2)CH2-	1S,2R	C ₅₃ H ₇₀ Cl ₂ F ₂ N ₂ O ₁₄
269766	3,4-(MeO)2-Ph	OMe	H	-C(F2)CH2-	1S,2R	C ₅₃ H ₇₀ Cl ₂ F ₂ N ₂ O ₁₄
269767	3,4-(MeO)2-Ph	H	H	-C(F2)CH2-	1S,2R	C ₅₂ H ₆₈ Cl ₂ F ₂ N ₂ O ₁₃
269768	3,4,5-(MeO)3-Ph	H	H	-CH(F)CH2-	1S,2S	C ₅₃ H ₇₁ Cl ₂ FN ₂ O ₁₄
269769	3,4-(MeO)2-Ph	H	H	-C(F2)CH2-	1R,2S	C ₅₂ H ₆₈ Cl ₂ F ₂ N ₂ O ₁₃
269770	3,4,5-(MeO)3-Ph	H	OMe	(Z)-C(F)=CH-	1S,2R	C ₅₄ H ₇₁ Cl ₂ FN ₂ O ₁₅

SOURCES – Cornell Research Foundation, Ithaca, NY (US); Glaxo Wellcome.

REFERENCES

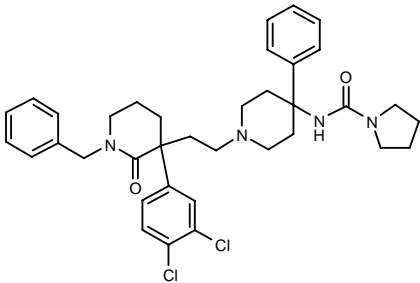
1. Bigham, E.C. et al. (Glaxo Wellcome plc;Cornell Research Foundation, Inc.) *Subst. isoquinolines as ultra short acting neuromuscular blockers*. WO 9842674, WO 9842675.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

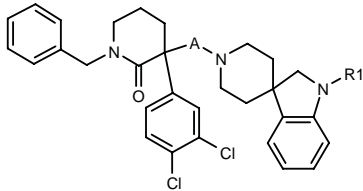
265101

N-[1-[2-[1-Benzyl-3-(3,4-dichlorophenyl)-2-oxopiperidin-3-yl]ethyl]-4-phenylpiperidin-4-yl]pyrrolidine-1-carboxamide

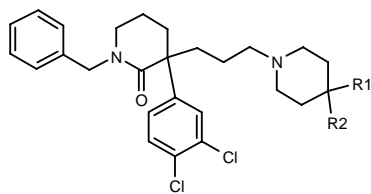


C36 H42 Cl2 N4 O2; Mol wt: 633.6598

ACTION – Potent and selective human neurokinin NK₃ receptor antagonist with a K_i value < 5 nM against [¹²⁵I]-His[MePhe⁷]-NKB binding to human cloned NK₃ receptors. Potentially useful in the treatment of conditions such as anxiety, asthma, depression, epilepsy, Parkinson's disease, schizophrenia, migraine and pain. A representative compound from a series of cyclic amide derivatives, wherein the following are also specifically claimed:



Compound	R1	A	Formula
267664	1-pyrrolidinyl-CO	-(CH2)2-	C ₃₇ H ₄₂ Cl ₂ N ₄ O ₂
267665	SO2Me	-(CH2)2-	C ₃₃ H ₃₇ Cl ₂ N ₃ O ₃ S
267668	SO2Me	-(CH2)3-	C ₃₄ H ₃₉ Cl ₂ N ₃ O ₃ S



Compound	R1	R2	Formula
267666	1-pyrrolidinyl-CONH	CH2Ph	C ₃₆ H ₄₆ Cl ₂ N ₄ O ₂
267667	1-pyrrolidinyl-CO	Ph	C ₃₇ H ₄₃ Cl ₂ N ₃ O ₂
267669	1-pyrrolidinyl-CO	CH2Ph	C ₃₆ H ₄₅ Cl ₂ N ₃ O ₂
267670	4-morpholinyl-CONHCH2	CH2Ph	C ₃₆ H ₄₈ Cl ₂ N ₄ O ₃
267671	4-morpholinyl-CO	CH2Ph	C ₃₆ H ₄₅ Cl ₂ N ₃ O ₃

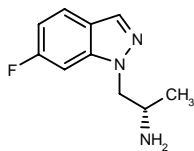
SOURCE – Sanofi.

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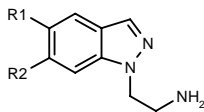
269067

1-(6-Fluorindazol-1-yl)propane-2(S)-amine



C10 H12 F N3; Mol wt: 193.2238

ACTION – Potent and selective 5-HT_{2C} receptor agonist with potential in the treatment of CNS disorders such as anxiety, depression, and sexual, appetite and sleep disorders. Compound exhibited a minimum effective dose (MED) of 0.03 mg/kg s.c. when tested in the rat penile erection assay. Other compounds from this series of aminoalkylindazole derivatives include the following:



Compound	R1	R2	Formula
269068	Cl	Cl	C ₉ H ₉ Cl ₂ N ₃
269069	F	H	C ₉ H ₁₀ FN ₃

SOURCE – Yamanouchi.

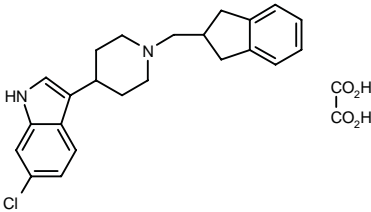
REFERENCES

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ANTIPSYCHOTIC DRUGS

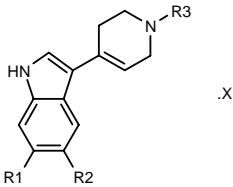
268771

6-Chloro-3-[1-(indan-2-ylmethyl)piperidin-4-yl]-1 H-indole oxalate

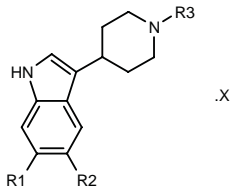


C23 H25 Cl N2 . C2 H2 O4; Mol wt: 454.9513

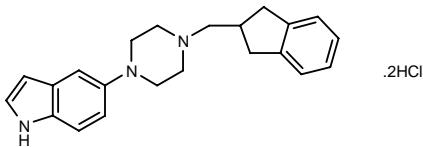
ACTION – Antipsychotic agent, a potent dopamine D₄ receptor antagonist with an IC₅₀ of 0.48 nM for inhibition of [³H]-YM-09151-2 binding to cloned human receptors and little or no affinity for dopamine D₂ receptors. Within this series of indane or dihydroindole derivatives, the following are also included:



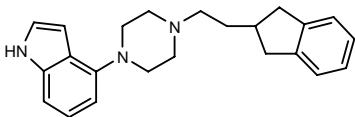
Compound	R1	R2	R3	X	Formula
268772	H	H	1-indanyl-CH2		C ₂₃ H ₂₄ N ₂
268774	Cl	H	1-indanyl-CH2CH2		C ₂₄ H ₂₅ ClN ₂
268775	H	F	1-indanyl-CH2CH2		C ₂₄ H ₂₅ FN ₂
268777	Cl	H	2-indanyl-CH2	oxalate	C ₂₃ H ₂₃ ClN ₂ .C ₂ H ₂ O ₄
268778	H	H	2-indanyl-CH2		C ₂₃ H ₂₄ N ₂



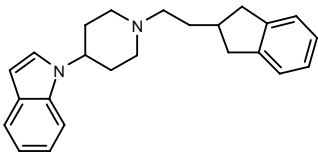
Compound	R1	R2	R3	X	Formula
268773	Cl	H	6-CN-1-indanyl-CH2	fumarate	C ₂₄ H ₂₄ ClN ₃ .C ₄ H ₄ O ₄
268776	H	F	1-indanyl-CH2CH2	oxalate	C ₂₄ H ₂₇ FN ₂ .C ₂ H ₂ O ₄
268780	H	H	2-indanyl-CH2		C ₂₃ H ₂₆ N ₂



268779: C22 H25 N3 . 2HCl



268781: C23 H27 N3



268782: C24 H28 N2

Certain compounds within the scope of the invention also inhibit 5-HT reuptake and act as 5-HT_{1A} and/or 5-HT_{2A} receptor ligands.

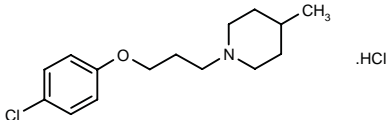
SOURCE – Lundbeck.

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1. Perregaard, J.K. et al. (Lundbeck A/S) *Indane or dihydroindole derivs.* WO 9828293.

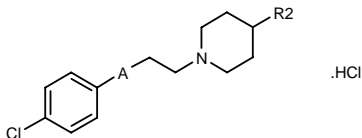
269348

1-[3-(4-Chlorophenoxy)propyl]-4-methylpiperidine hydrochloride



C15 H22 Cl N O . HCl; Mol wt: 304.2587

ACTION – Agent for the treatment of CNS disorders and neuropathies with potent and selective affinity for σ -receptors (IC₅₀ = 0.6 ng/ml) relative to dopamine D₂ receptors (IC₅₀ > 1000 ng/ml). A representative compound from a series of alkylamine derivatives, wherein the following are also included:



Compound	A	R2	Formula
269349	(E)-CH=CH-	H	C ₁₅ H ₂₀ ClN.HCl
269350	-OCH2-	Ph	C ₂₀ H ₂₄ ClNO.HCl
269351	(E)-CH=CH-	CH2CH2OH	C ₁₇ H ₂₄ ClNO.HCl
269352	-SCH2-	H	C ₁₄ H ₂₀ ClNS.HCl

SOURCE – Sumitomo Pharmaceuticals.

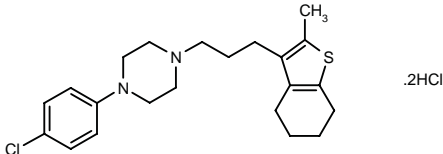
REFERENCES

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Y-36074

269056

1-(4-Chlorophenyl)-4-[3-(2-methyl-4,5,6,7-tetrahydro-benzo[*b*]thien-3-yl)propyl]piperazine dihydrochloride



C22 H29 Cl N2 S . 2HCl ; Mol wt: 461.9259

ACTION – Antipsychotic agent, a potent dopamine D₄ receptor antagonist (K_i = 0.50 nM) with selectivity over D₂ receptors (K_i = 170 nM). Compound exhibited good oral bioavailability in rats (> 30%) following administration of 30 mg/kg p.o., and it was shown to cross the blood–brain barrier. No mortality was observed in rats following single doses of 1000 mg/kg p.o. or repeated administration of 100 mg/kg p.o. for 10 days; additionally, no signs of toxicity were observed following repeated administration of 30 mg/kg p.o. for 10 days to dogs. Also reported to be useful for the treatment of alcohol dependence and drug abuse.

SOURCE – Yoshitomi.

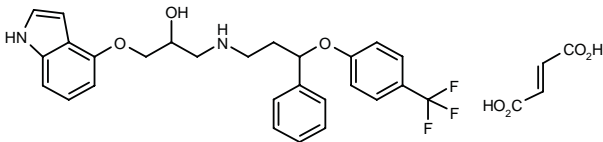
REFERENCES

1. Kuroita, T. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Thiophene cpds. and medicinal use thereof.* WO 9831679.

ANTIDEPRESSANTS

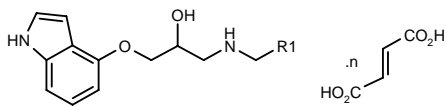
266173¹

1-(1*H*-Indol-4-yloxy)-3-[3-phenyl-3-[4-(trifluoromethyl)-phenoxy]propylamino]-2-propanol fumarate

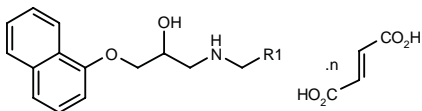


C27 H27 F3 N2 O3 . C4 H4 O4; Mol wt: 600.5869

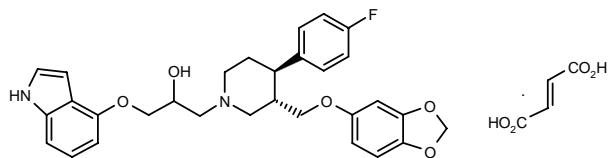
ACTION – A 5-HT_{1A} receptor antagonist and 5-HT reuptake inhibitor with additional activity as a β -blocker, claimed for the treatment of depression, anxiety, obsessive–compulsive disorders, panic attacks, alcohol and tobacco addiction, sexual dysfunction, sleep disorders and migraine. Within this series of aromatic amino alcohols, the following are also included:



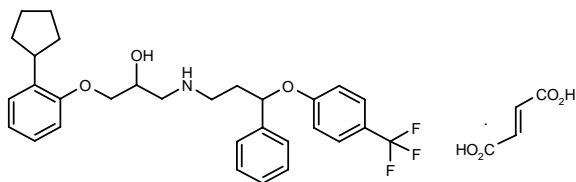
Compound	R1	Isomer	n	Formula
266929 ¹	(S)-4-CF3-PhOCH(Ph)CH2	R	1	C ₂₇ H ₂₇ F ₃ N ₂ O ₃ .C ₄ H ₄ O ₄
266930 ^{1,2}	(S)-4-CF3-PhOCH(Ph)CH2	S	1	C ₂₇ H ₂₇ F ₃ N ₂ O ₃ .C ₄ H ₄ O ₄
266934 ¹	cis-2-[N(Et)2CO]- -2-Ph-1-cyclopropyl		1	C ₂₆ H ₃₃ N ₂ O ₄ .C ₄ H ₄ O ₄
266935 ¹	4(R)-(4-F-Ph)-3-(S)-(1,3- -benzodioxol-5-yl-OCH2)-1-Pip		2	C ₃₆ H ₄₄ FN ₃ O ₅ .2C ₄ H ₄ O ₄



Compound	R1	Isomer	n	Formula
266936 ¹	4(R)-(4-F-Ph)-3-(S)-(1,3- -benzodioxol-5-yl-OCH2)-1-Pip		2	C ₃₈ H ₄₅ FN ₂ O ₅ .2C ₄ H ₄ O ₄
266937 ¹	(S)-4-CF3-PhOCH(Ph)CH2		1	C ₂₈ H ₂₈ F ₃ NO ₃ .C ₄ H ₄ O ₄
266938 ¹	(S)-4-CF3-PhOCH(Ph)CH2	S	1	C ₂₈ H ₂₈ F ₃ NO ₃ .C ₄ H ₄ O ₄
266939 ¹	(S)-4-CF3-PhOCH(Ph)CH2	R	1	C ₂₈ H ₂₈ F ₃ NO ₃ .C ₄ H ₄ O ₄
266940 ¹	4-CF3-PhOCH(Ph)- CH2CH2NH(CH2)4		2	C ₃₄ H ₃₆ F ₃ N ₂ O ₃ .2C ₄ H ₄ O ₄



Compound	Isomer	Formula
266931 ¹		C ₃₀ H ₃₁ FN ₂ O ₅ .C ₄ H ₄ O ₄
266932 ¹	S	C ₃₀ H ₃₁ FN ₂ O ₅ .C ₄ H ₄ O ₄
266933 ^{1,2}	R	C ₃₀ H ₃₁ FN ₂ O ₅ .C ₄ H ₄ O ₄



266941¹: C30 H34 F3 N O3 . C4 H4 O4

SOURCE – Pierre Fabre.

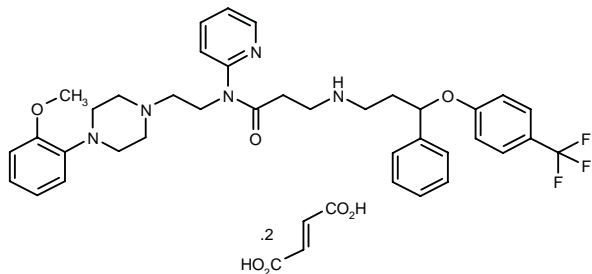
REFERENCES

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2. Perez, M. et al. *Design and synthesis of new potent, silent 5-HT_{1A} antagonists by covalent coupling of aminopropanol derivatives with selective serotonin reuptake inhibitors*. Bioorg Med Chem Lett 1998, 8(23): 3423.

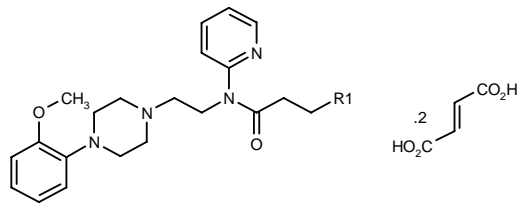
266176

N-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-*N*-(2-pyridyl)-3-[2-[4-(trifluoromethyl)phenoxy]-2-phenylethyl-amino]propionamide difumarate



C37 H42 F3 N5 O3 . 2 C4 H4 O4; Mol wt: 893.9080

ACTION – A 5-HT_{1A} receptor antagonist and 5-HT reuptake inhibitor with potential in the treatment of depression, anxiety, obsessive–compulsive disorder, panic attacks, alcohol and tobacco addiction, sexual dysfunction and sleep disorders. Within this series of aromatic amines of arylpiperazines, the following are also included:



Compound	R1	Formula
266889	4-CF3-PhOCH(Ph)- CH2CH2NHCH2CH2	C ₃₉ H ₄₆ F ₃ N ₅ O ₃ .2C ₄ H ₄ O ₄
266890	4-CF3-PhOCH(Ph)- CH2CH2NH(CH2)3	C ₄₀ H ₄₈ F ₃ N ₅ O ₃ .2C ₄ H ₄ O ₄
266891	cis-2-[N(Et)2CO]-2-Ph- -1-cyclopropyl-CH2NH	C ₃₆ H ₄₈ N ₆ O ₃ .2C ₄ H ₄ O ₄
266892	cis-2-[N(Et)2CO]-2-Ph- -1-cyclopropyl-CH2NHCH2CH2	C ₃₈ H ₅₂ N ₆ O ₃ .2C ₄ H ₄ O ₄
266893	cis-2-[N(Et)2CO]-2-Ph- -1-cyclopropyl-CH2NH(CH2)3	C ₃₉ H ₅₄ N ₆ O ₃ .2C ₄ H ₄ O ₄

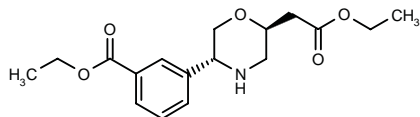
SOURCE – Pierre Fabre.

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1. Halazy, S. and Perez, M. (Pierre Fabre Médicament) *Aromatic amines or arylpiperazines, their preparation and application as medicine*. WO 9823590.

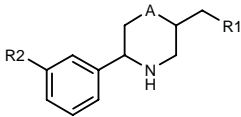
268957

trans-3-[6-(Ethoxycarbonylmethyl)morpholin-3-yl]benzoic acid ethyl ester



C17 H23 N O5; Mol wt: 321.3707

ACTION – Compound with high affinity for and good antagonist activity at GABA_B receptors. It is reported to antagonize the effects of both endogenous GABA and baclofen. Potentially useful as an antidepressant, nootropic and anxiolytic agent, for the treatment of cognitive disorders, schizophrenia and myopia, and as an antidote to baclofen. A compound within a series of (thio)morpholine-substituted carboxylic and phosphinic acid derivatives, wherein the following are also included:



Compound	R1	R2	A	Isomer	Formula
268958	CO2Et	CO2Et	O	cis	C ₁₇ H ₂₃ NO ₅
268959	CO2Na	CO2Na	O	trans	C ₁₃ H ₁₃ NNa ₂ O ₅
268960	CO2H	CO2Na	O	cis	C ₁₃ H ₁₄ NNaO ₅
268961	CO2Et	Br	S	cis	C ₁₄ H ₁₈ BrNO ₂ S
268962	CO2Et	Br	S	trans	C ₁₄ H ₁₈ BrNO ₂ S
268963	CO2Et	CO2Et	S	cis	C ₁₇ H ₂₃ NO ₄ S
268964	CO2Et	CO2Et	S	trans	C ₁₇ H ₂₃ NO ₄ S
268965	CO2Na	CO2Na	S	cis	C ₁₃ H ₁₃ NNa ₂ O ₄ S
268966	CO2Na	CO2Na	S	trans	C ₁₃ H ₁₃ NNa ₂ O ₄ S
268967	CO2Na	Br	S	trans	C ₁₂ H ₁₃ BrNNaO ₂ S
268968	cyclohexyl-CH2PO(OEt)	Br	S	cis	C ₂₀ H ₃₁ BrNO ₂ PS
268969	cyclohexyl-CH2PO(OEt)	Br	S	trans	C ₂₀ H ₃₁ BrNO ₂ PS
268970	cyclohexyl-CH2PO(OH)	Br	S		C ₁₈ H ₂₇ BrNO ₂ PS
268971	cyclohexyl-CH2PO(OEt)	CO2Me	S		C ₂₂ H ₃₄ NO ₄ PS
268972	cyclohexyl-CH2PO(ONa)	CO2Na	S		C ₁₉ H ₂₆ NNa ₂ O ₄ PS

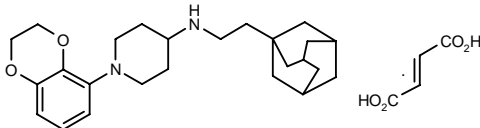
SOURCE – Novartis.

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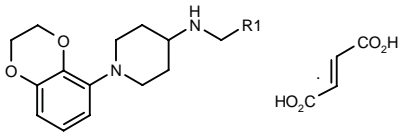
269074

N-[2-(1-Adamantyl)ethyl]-*N*-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperidin-4-yl]amine fumarate



C25 H36 N2 O2 . C4 H4 O4; Mol wt: 512.6430

ACTION – Agent with high affinity and selectivity for 5-HT_{1B} receptors (pK_i = 8.0 against [³H]-GR-125743 binding in guinea pig striatum preparations) relative to 5-HT_{1A} receptors, potentially useful for the treatment of depression, obesity, migraine, anxiety, schizophrenia, cognition disorders, etc. Within this series of specifically claimed *N*-aryl piperidine derivatives, the following are also included:



Compound	R1	Formula
269075	1-benzocyclobutenyl	C ₂₂ H ₂₄ N ₂ O ₂ .C ₄ H ₄ O ₄
269076	8,9-(MeO)2-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl	C ₂₉ H ₃₅ N ₃ O ₄ .C ₄ H ₄ O ₄

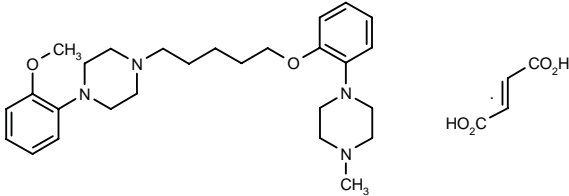
SOURCE – ADIR.

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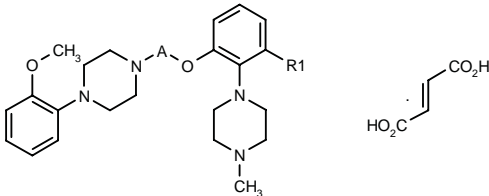
269798

1-(2-Methoxyphenyl)-4-[5-[2-(4-methylpiperazin-1-yl)-phenoxy]pentyl]piperazine fumarate



C27 H40 N4 O2 . C4 H4 O4; Mol wt: 568.7106

ACTION – A human 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist (K_i = 8.6, 2.6 and 11 nM, respectively) with good selectivity relative to 5-HT_{1C}, 5-HT₂ and dopamine D₂ receptors, as well as α₁- and α₂-adrenoceptors. Claimed for the treatment or prevention of depression, obsessive-compulsive disorder, anxiety, panic attacks, schizophrenia, bulimia, alcoholism, pain and neurodegenerative disorders such as Parkinson's disease or Alzheimer's disease. Compound is also reported to be able to control the growth and proliferation of C6 glial cells transfected with the 5-HT_{1D} and 5-HT_{1B} receptor genes when stimulated with 5-HT and is therefore also claimed for the treatment or prevention of cancer. Within this series of piperazine derivatives, the following are also included:



Compound	R1	A	Formula
269799	Me	-(CH2)5-	C ₂₈ H ₄₂ N ₄ O ₂ .C ₄ H ₄ O ₄
269800	H	-(CH2)7-	C ₂₉ H ₄₄ N ₄ O ₂ .C ₄ H ₄ O ₄

SOURCE – Pierre Fabre.

REFERENCES

1. Halazy, S. et al. (Pierre Fabre Médicament) *Piperazines derived from cyclic amines, preparation and application thereof as medicines.* WO 9842692.

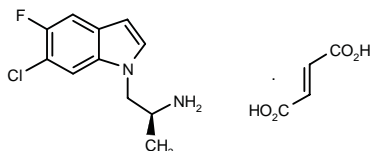
RO-60-0175

257630

224908 (as racemic)*

2(S)-1-(6-Chloro-5-fluoro-1*H*-indol-1-yl)-2-propanamine fumarate

Org-35030



C11 H12 Cl F N2 . C4 H4 O4; Mol wt: 342.7524

ACTION – Selective 5-HT_{2C} receptor agonist with high-affinity binding to the human receptor ($pK_i = 9.0$) and considerably lower affinity for other 5-HT receptor subtypes and numerous nonserotonergic receptors. *In vivo*, it elicited penile erection in rats, indicating a 5-HT_{2C} agonist profile, and it significantly reduced compulsive burying behavior in mice, excessive consumption of palatable foods in nondeprived rats and excessive drinking in rats. Its antidepressant potential was demonstrated by reduction in learning deficits induced by olfactory bulbectomy in rats. Compound at pharmacological doses was devoid of side effects in squirrel monkeys, and it did not exhibit anxiolytic or anxiogenic effects in rats. No tolerance developed to its ability to inhibit excessive whole-body scratching induced by 8-OH-DPAT in squirrel monkeys after 2 weeks of treatment. This profile suggests potential utility in the treatment of obsessive-compulsive behavior and/or depression.

SOURCES – Organon; Roche.

REFERENCES

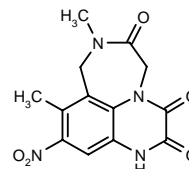
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- Martin, J.R. et al. *5-HT_{2C} receptor agonists: Pharmacological characteristics and therapeutic potential.* J Pharmacol Exp Ther 1998, 286(2): 913.
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- Zhang, Y. et al. *Characterisation of the 5-HT_{2C} receptor agonist RO 60-0175 in cells expressing the human 5-HT_{2C} receptor.* Soc Neurosci Abstr 1998, 24(Part 2): Abstr 541.14.

*Drug Data Report 1995, 017(10): 0888.

NEUROLOGIC DRUGS

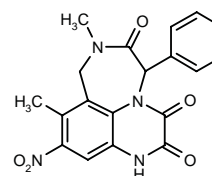
ANTIEPILEPTIC DRUGS

269184

7,9-Dimethyl-10-nitro-2,3,5,6,7,8-hexahydro-1*H*-pyrazino[3,2,1-*jk*][1,4]benzodiazepine-2,3,6-trione

C13 H12 N4 O5; Mol wt: 304.2608

ACTION – Neuroprotective agent, an excitatory amino acid receptor antagonist that acts at NMDA (glycine site), AMPA and kainate receptors ($IC_{50} = 0.2, 0.5$ and $1.55 \mu M$, respectively). *In vivo* activity was demonstrated in the maximal electroshock assay in mice, where it gave a maximum protection of 80% at about 15 min after a dose of 30 mg/kg i.v., rapidly falling to 20% at 30 min; when the compound was administered at 10 mg/kg i.v. to mice pretreated with probenecid (200 mg/kg i.p.), complete (100%) protection was observed for > 60 min. Another compound from this series of tricyclic quinoxaline derivatives is:



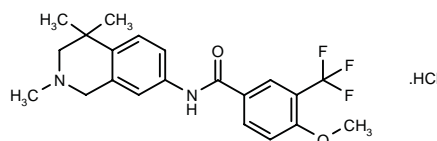
269185: C19 H16 N4 O5

SOURCE – Warner-Lambert.

REFERENCES

- Nikam, S.S. (Warner-Lambert Co.) *Tricyclic quinoxaline derivs. as neuroprotective agents.* WO 9827097.

269241

4-Methoxy-3-(trifluoromethyl)-*N*-(2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)benzamide hydrochloride

C21 H23 F3 N2 O2 . HCl; Mol wt: 428.8796

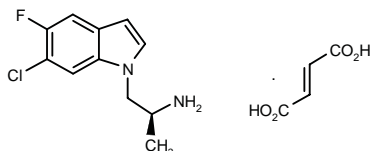
RO-60-0175

257630

224908 (as racemic)*

2(S)-1-(6-Chloro-5-fluoro-1*H*-indol-1-yl)-2-propanamine fumarate

Org-35030



C11 H12 Cl F N2 . C4 H4 O4; Mol wt: 342.7524

ACTION – Selective 5-HT_{2C} receptor agonist with high-affinity binding to the human receptor ($pK_i = 9.0$) and considerably lower affinity for other 5-HT receptor subtypes and numerous nonserotonergic receptors. *In vivo*, it elicited penile erection in rats, indicating a 5-HT_{2C} agonist profile, and it significantly reduced compulsive burying behavior in mice, excessive consumption of palatable foods in nondeprived rats and excessive drinking in rats. Its antidepressant potential was demonstrated by reduction in learning deficits induced by olfactory bulbectomy in rats. Compound at pharmacological doses was devoid of side effects in squirrel monkeys, and it did not exhibit anxiolytic or anxiogenic effects in rats. No tolerance developed to its ability to inhibit excessive whole-body scratching induced by 8-OH-DPAT in squirrel monkeys after 2 weeks of treatment. This profile suggests potential utility in the treatment of obsessive-compulsive behavior and/or depression.

SOURCES – Organon; Roche.

REFERENCES

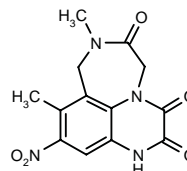
- Bös, M. (F. Hoffmann-La Roche AG) 1-Aminoethylindoles. CA 2132883, EP 655440, US 5494928.
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- Zhang, Y. et al. *Characterisation of the 5-HT_{2C} receptor agonist RO 60-0175 in cells expressing the human 5-HT_{2C} receptor.* Soc Neurosci Abst 1998, 24(Part 2): Abst 541.14.

*Drug Data Report 1995, 017(10): 0888.

NEUROLOGIC DRUGS

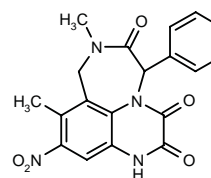
ANTIEPILEPTIC DRUGS

269184

7,9-Dimethyl-10-nitro-2,3,5,6,7,8-hexahydro-1*H*-pyrazino[3,2,1-*jk*][1,4]benzodiazepine-2,3,6-trione

C13 H12 N4 O5; Mol wt: 304.2608

ACTION – Neuroprotective agent, an excitatory amino acid receptor antagonist that acts at NMDA (glycine site), AMPA and kainate receptors ($IC_{50} = 0.2, 0.5$ and $1.55 \mu M$, respectively). *In vivo* activity was demonstrated in the maximal electroshock assay in mice, where it gave a maximum protection of 80% at about 15 min after a dose of 30 mg/kg i.v., rapidly falling to 20% at 30 min; when the compound was administered at 10 mg/kg i.v. to mice pretreated with probenecid (200 mg/kg i.p.), complete (100%) protection was observed for > 60 min. Another compound from this series of tricyclic quinoxaline derivatives is:



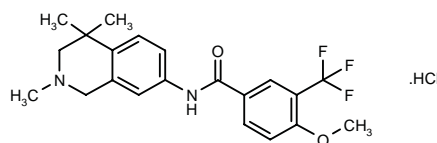
269185: C19 H16 N4 O5

SOURCE – Warner-Lambert.

REFERENCES

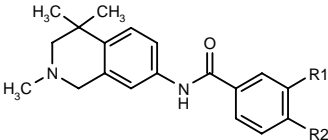
- Nikam, S.S. (Warner-Lambert Co.) *Tricyclic quinoxaline derivs. as neuroprotective agents.* WO 9827097.

269241

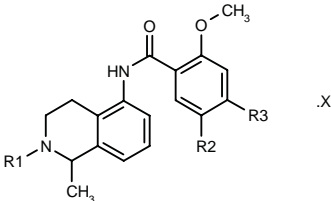
4-Methoxy-3-(trifluoromethyl)-*N*-(2,4,4-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)benzamide hydrochloride

C21 H23 F3 N2 O2 . HCl; Mol wt: 428.8796

ACTION – Anticonvulsant with affinity for a novel receptor site in rat forebrain labeled by [³H]-SB-204269 (pK_i = 8.5), proven active *in vivo* in the maximal electroshock seizure (MES) test in rats, giving a 510% increase in CC₅₀ (current required to induce a tonic seizure in 50% of animals) at 2 h after a dose of 2 mg/kg p.o. Other specifically claimed isoquinolyl-benzamide derivatives include the following:



Compound	R1	R2	Formula
269242	CN	i-Pr	C ₂₃ H ₂₇ N ₃ O
269243	Br	Et	C ₂₁ H ₂₅ BrN ₂ O
269244	Br	OEt	C ₂₁ H ₂₅ BrN ₂ O ₂
269245	Cl	i-PrO	C ₂₂ H ₂₇ ClN ₂ O ₂



Compound	R1	R2	R3	X	Formula
269246	H	Cl	OEt	CF ₃ CO ₂ H	C ₂₂ H ₂₃ ClN ₂ O ₃ ·C ₂ HF ₃ O ₂
269247	Me	Br	OMe	HCl	C ₂₀ H ₂₃ BrN ₂ O ₃ ·HCl
269248	Me	Cl	OEt	HCl	C ₂₁ H ₂₅ Cl ₂ N ₂ O ₃ ·HCl
269249	Me	Cl	i-PrO	HCl	C ₂₂ H ₂₇ ClN ₂ O ₃ ·HCl
269250	Me	H	t-Bu	HCl	C ₂₃ H ₃₀ N ₂ O ₂ ·HCl
269251	Me	CF ₃	Me	HCl	C ₂₁ H ₂₃ F ₃ N ₂ O ₂ ·HCl

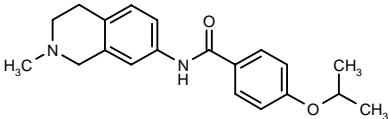
SOURCE – SmithKline Beecham.

REFERENCES

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269260

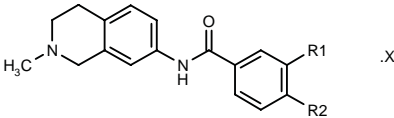
4-Isopropoxy-*N*-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)benzamide



C20 H24 N2 O2; Mol wt: 324.4216

ACTION – Anticonvulsant also claimed for the treatment or prevention of a broad range of disorders including anxiety, depression, mania, drug and alcohol withdrawal symptoms, migraine, psychosis, Parkinson’s disease, Alzheimer’s disease, cerebral ischemia, sleep disorders, traumatic brain injury and neuropathic pain. Compound exhibited high affinity for the [³H]-SB-204269 binding site in rat forebrain membranes (pK_i > 7). Anticonvulsant activity was demonstrated in the maximal electroshock seizure (MES) test in mice, where it produced a 90% increase in seizure threshold at 10 mg/kg p.o. Within this

series of substituted isoquinoline derivatives, the following are also included:



Compound	R1	R2	X	Formula
269261	Cl	H		C ₁₇ H ₁₇ ClN ₂ O
269262	H	t-Bu		C ₂₁ H ₂₆ N ₂ O
269263	H	OPh		C ₂₃ H ₂₂ N ₂ O ₂
269264	Cl	i-PrO		C ₂₀ H ₂₃ ClN ₂ O ₂
269265	Br	OEt		C ₁₉ H ₂₁ BrN ₂ O ₂
269266	CF ₃	OMe		C ₁₉ H ₁₉ F ₃ N ₂ O ₂
269267	CN	i-Pr	HCl	C ₂₁ H ₂₃ N ₃ O·HCl

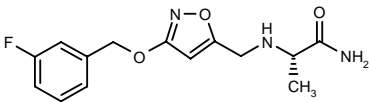
SOURCE – SmithKline Beecham.

REFERENCES

1. Thompson, M. et al. (SmithKline Beecham plc) *Substd. isoquinoline derivs. and their use as anticonvulsants.* WO 9841508.

269467

N’-[3-(3-Fluorobenzoyloxy)isoxazol-5-ylmethyl]-L-alaninamide



C14 H16 F N3 O3; Mol wt: 293.2964

ACTION – Anticonvulsant and neuroprotective agent from a series of 2-[(3-substituted)-5-isoxazolylmethylamino]-alkanamide derivatives, also reported to be useful as an antidepressant, antiparkinsonian, antispastic and/or hypnotic agent.

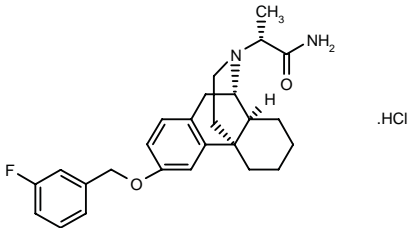
SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *2-[(3-Substd.)-5-isoxazolylmethyl-amino]alkanamide derivs.* WO 9843964.

269621

N-[1(*R*)-Carbamoyl-ethyl]-3-(3-fluorobenzoyloxy)-*ent*-morphinan hydrochloride



C26 H31 F N2 O2 . HCl; Mol wt: 459.0018

ACTION – Agent for the treatment of CNS disorders such as epilepsy, Parkinson's disease, neuronal loss associated with stroke, ischemia, hypoxia, CNS trauma, hypoglycemia or surgery and neurodegenerative diseases such as Alzheimer's disease and other types of dementia, amyotrophic lateral sclerosis, Down's syndrome and Huntington's disease, as well as for use as an antidepressant, hypnotic and antispastic agent. A representative compound from a series of aralkoxy-morphinan derivatives.

SOURCE – Pharmacia & Upjohn.

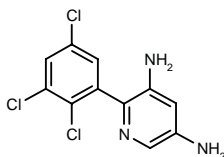
REFERENCES

1. Varasi, M. et al. (Pharmacia & Upjohn SpA) *Aralkoxy-morphinan derivs. for treatment of CNS disorders*. WO 9843961.

GW-273295

267797

2-(2,3,5-Trichlorophenyl)pyridine-3,5-diamine



C11 H8 Cl3 N3; Mol wt: 288.5642

ACTION – Sodium channel blocker from a series of lamotrigine derivatives, with potential as an antiepileptic agent.

SOURCE – Glaxo Wellcome.

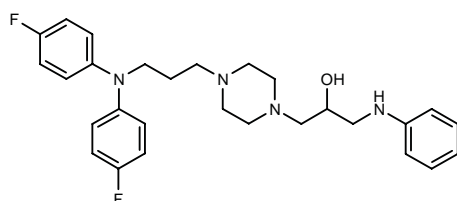
REFERENCES

1. Shah, G.P. et al. *Sodium channel inhibitors 2: Structure activity relationships of the lamotrigine series*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.192.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

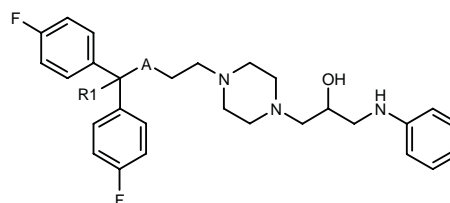
268791

1-[4-[3-[Bis(4-fluorophenyl)amino]propyl]piperazin-1-yl]-3-(phenylamino)-2-propanol

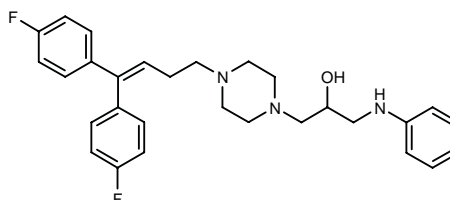


C28 H34 F2 N4 O; Mol wt: 480.5996

ACTION – Dopamine reuptake inhibitor ($IC_{50} = 1.83$ nM [3H]-GBR-12935 binding in rat striatum membrane preparations) potentially useful for the treatment of Parkinson's disease. Other related compounds include the following:



Compound	R1	A	Formula
268792	OH	CH2	C ₂₉ H ₃₅ F ₂ N ₃ O ₂
268794	H	O	C ₂₈ H ₃₃ F ₂ N ₃ O ₂



268793: C₂₉ H₃₃ F₂ N₃ O

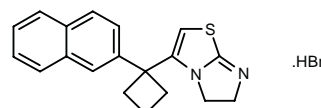
SOURCE – Pola Chemical.

REFERENCES

1. Namiki, T. et al. (Pola Chemical Industries Inc.) *Inhibitors of dopamine reabsorption*. JP 98218867.

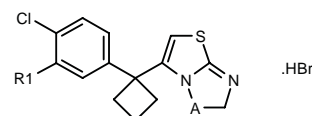
269291

3-[1-(2-Naphthyl)cyclobutyl]-5,6-dihydroimidazo[2,1-b]-thiazole hydrobromide



C₁₉ H₁₈ N₂ S . HBr ; Mol wt: 387.3431

ACTION – An inhibitor of the neuronal reuptake of 5-HT, norepinephrine and dopamine, as demonstrated *in vitro* in receptor binding assays using frontal cortical tissue or striatal tissue preparations from rat brain ($K_i = 25$, 4.4 and 5.9 nM, respectively), particularly useful for the treatment of Parkinson's disease, as well as depression, anxiety, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy and as a neuroprotective agent for stroke. Within this series of specifically claimed substituted 4-arylmethylene-2-imino-2,3-dihydrothiazole derivatives, the following are also included:



Compound	R1	A	Formula
269292	Cl	-CH2-	C ₁₅ H ₁₄ Cl ₂ N ₂ S.HBr
269293	H	-(CH ₂) ₂ -	C ₁₆ H ₁₇ ClN ₂ S.HBr
269294	H	-CH2-	C ₁₅ H ₁₅ ClN ₂ S.HBr
269295	Cl	-(CH ₂) ₂ -	C ₁₆ H ₁₆ Cl ₂ N ₂ S.HBr

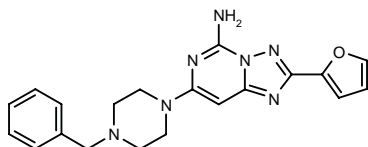
SOURCE – Knoll.

REFERENCES

1. Cheetham, S.C. et al. (Knoll AG) *Substd. 4-arylmethylene-2-imino-2,3-dihydro-thiazoles and derivs. and their pharmaceutical use.* WO 9841528.

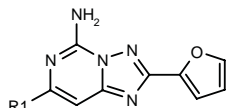
269450

7-(4-Benzylpiperazin-1-yl)-2-(2-furyl)-1,2,4-triazolo[1,5-c]-pyrimidine-5-amine



C₂₀ H₂₁ N₇ O; Mol wt: 375.4339

ACTION – Adenosine A_{2a} receptor antagonist for the treatment of Parkinson's disease and senile dementia from a series of [1,2,4]triazolo[1,5-c]pyrimidine derivatives, wherein the following are also included:



Compound	R1	Formula
269451	3,4-(MeO)2-PhO	C ₁₇ H ₁₅ N ₅ O ₄
269452	4-morpholinyl	C ₁₃ H ₁₄ N ₆ O ₂
269453	4-Me-1-Piz	C ₁₄ H ₁₇ N ₇ O

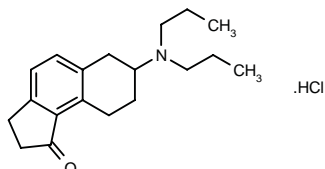
SOURCE – Kyowa Hakko.

REFERENCES

1. Tsumuki, H. et al. (Kyowa Hakko Kogyo Co., Ltd.) *[1,2,4]Triazolo[1,5-c]pyrimidine derivs.* WO 9842711.

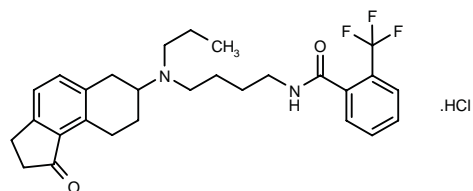
269495

7-(Dipropylamino)-2,3,6,7,8,9-hexahydro-1H-benzo-[e]inden-1-one hydrochloride



C₁₉ H₂₇ N O . HCl; Mol wt: 321.8892

ACTION – Antiparkinsonian and antipsychotic agent with specific binding affinity for dopamine D₃ receptors (pK_i = 8.0 for inhibition of [¹²⁵I]-iodosulpride binding in CHO cells expressing human receptor) compared to D₂ receptors. Another specifically claimed indene derivative is:



269496: C₂₈ H₃₃ F₃ N₂ O₂ . HCl

SOURCE – ADIR.

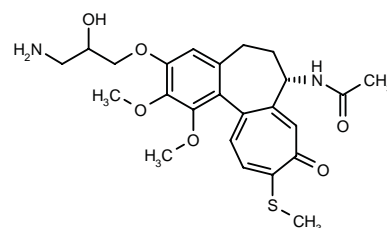
REFERENCES

1. Millan, M. and Peglion, J.-L. (ADIR et Cie.) *Aminated 6,7,8,9-tetrahydro-cyclopenta[a]naphthalene- and 2,3-dihydro-cyclopenta[e]indene-derivs., process for their preparation and pharmaceutical compsns. containing them.* EP 870759, JP 98287631.

ANTISPASTIC DRUGS AND DRUGS FOR MUSCLE SPASMS

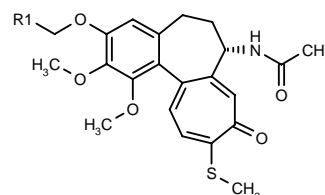
269471

7(S)-Acetamido-3-(3-amino-2-hydroxypropoxy)-1,2-dimethoxy-10-(methylsulfonyl)-5,6,7,9-tetrahydrobenzo-[a]heptalen-9-one



C₂₄ H₃₀ N₂ O₆ S; Mol wt: 474.5750

ACTION – Muscle relaxant and antiinflammatory agent whose antispastic action is attributed to its glycine-mimetic activity via an interaction with strychnine-sensitive glycine receptors. *In vivo*, the compound produced 65% inhibition of polysynaptic reflexes induced by strychnine in rabbits at a dose of 1 mg/kg i.m., being more potent than the reference compound thiocolchicoside (comparable effects only at 5 mg/kg i.m.), as well as less toxic: LD₅₀ > 30 mg/kg i.v. vs. 7.5 mg/kg i.v. Potentially useful for the treatment of pain associated with inflammatory–rheumatic and degenerative orthopedic pathologies. Other exemplified thiocolchicine derivatives include the following:



Compound	R1	Formula
269472	2-oxiranyl	C ₂₄ H ₂₇ NO ₆ S
269473	CH(OH)CH ₂ OH	C ₂₄ H ₂₈ NO ₇ S

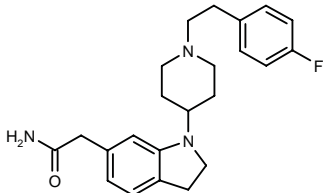
SOURCE – Indena.

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1. Bombardelli, E. (Indena SpA) *Thiocolchicine derivs. with antiinflammatory and muscle relaxant activities.* EP 870761.

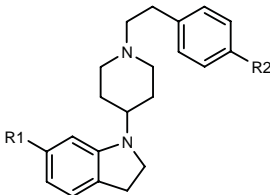
269670

2-[1-[1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl]indolin-6-yl]acetamide

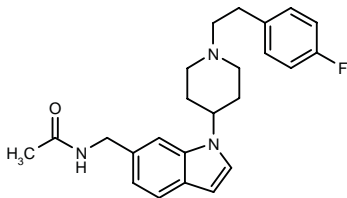


C23 H28 F N3 O; Mol wt: 381.4922

ACTION – Potent 5-HT_{1A} and 5-HT₂ receptor antagonist, as demonstrated in binding studies by K_i values of 1.31 and 0.77 nM, respectively, for inhibition of [³H]-8-OH-DPAT binding in rat hippocampus and [³H]-ketanserin binding in rat cerebral cortex. Potentially useful for the treatment or prevention of spastic paralysis or as a central muscle relaxant for alleviating myotonia. A representative compound from a series of 1,4-substituted cyclic amine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
269671	H	CH2NHAc	C ₂₄ H ₃₁ N ₃ O
269672	CONH2	F	C ₂₂ H ₂₆ FN ₃ O
269673	CH2NHAc	F	C ₂₄ H ₃₀ FN ₃ O
269674	CH2CONHEt	F	C ₂₅ H ₃₂ FN ₃ O



269675: C24 H28 F N3 O

SOURCE – Eisai.

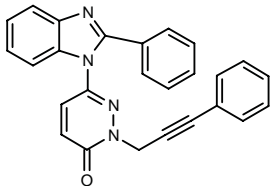
REFERENCES

1. Kitazawa, N. et al. (Eisai Co., Ltd.) *1,4-Substd. cyclic amine derivs.* WO 9843956.

COGNITION-ENHANCING DRUGS

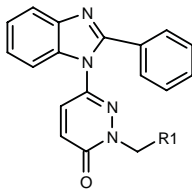
267853

6-(2-Phenylbenzimidazol-1-yl)-2-(3-phenyl-2-propynyl)-pyridazin-3(2H)-one



C26 H18 N4 O; Mol wt: 402.4552

ACTION – Adenosine A₁ antagonist (K_i = 9.9 nM or less against [³H]-CHA binding in rat frontal cortex) with potential in the treatment of Alzheimer's disease, depression, heart failure, hypertension, arrhythmias, renal failure, nephritis, nephrotic syndrome, edema, obesity and gout. Within this series of pyridazin-3-one derivatives, the following are also included:



Compound	R1	Formula
267854	CH2CH2CO2Et	C ₂₃ H ₂₂ N ₄ O ₃
267855	3-MeO-Ph	C ₂₅ H ₂₀ N ₄ O ₂
267856	CH2CH2CO2H	C ₂₁ H ₁₈ N ₄ O ₃
267857	(CH2)3OH	C ₂₁ H ₂₀ N ₄ O ₂

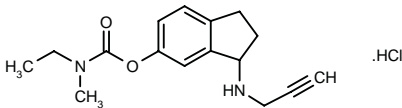
SOURCE – Toa Eiyo.

REFERENCES

1. Kamimoto, K. et al. (Toa Eiyo Ltd.) *Pyridadinone derivs., their preparation method adenosine A₁ antagonists containing the same.* JP 98182636.

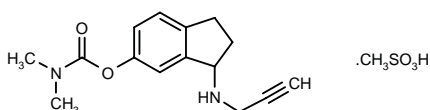
268252

N-Ethyl-N-methylcarbamic acid 1-(2-propynylamino)-indan-6-yl ester hydrochloride



C16 H20 N2 O2 . HCl; Mol wt: 308.8069

ACTION – Agent for the treatment of CNS disorders such as depression, attention deficit hyperactivity disorder, Tourette's syndrome, Alzheimer's disease and other dementias, as well as neurotraumatic disorders such as stroke, hypoxia, anoxia, head or spinal cord trauma and peripheral neuropathy, that acts by inhibiting acetylcholinesterase (AChE) and monoamine oxidase (MAO). Compound inhibited AChE both *in vitro* ($IC_{50} = 53.0 \mu M$) and *ex vivo* in mice ($ID_{50} = 140.0 \mu mol/kg$ s.c.). In addition, it was shown to inhibit MAO *in vivo* with selectivity for MAO enzyme subtypes in the brain in preference to the periphery; in the brain, it inhibited MAO-A by 75 and 70% at 50 mg/kg s.c. or p.o., respectively, and MAO-B by 85 and 80% at 50 mg/kg s.c. or p.o., respectively. Compound was found to improve neurological score in several *in vivo* models of hypoxia, ischemia and head injury. LD_{50} in mice is 1400 $\mu mol/kg$ s.c. Another compound from this series of aminoindan derivatives is:



268253: C₁₅ H₁₈ N₂ O₂ . C₄ H₄ O₃ S

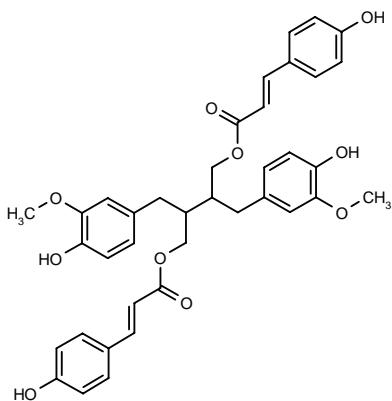
SOURCES – Teva; Yissum.

REFERENCES

1. Chorev, M. et al. (Teva Pharmaceutical Industries Ltd.; Yisum Research Development Co.) *Aminoindan derivs.* WO 9827055.

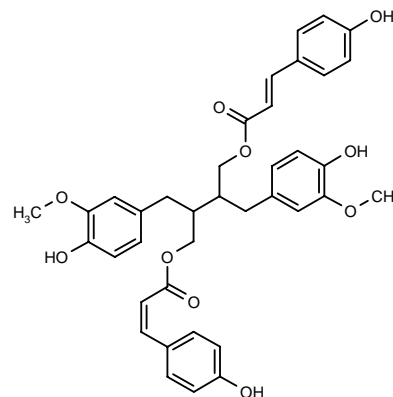
268374

2,3-Bis(4-hydroxy-3-methoxybenzyl)butane-1,4-diol 1-O,4-O-bis[3-(4-hydroxyphenyl)-2(E)-propenoyl] ester

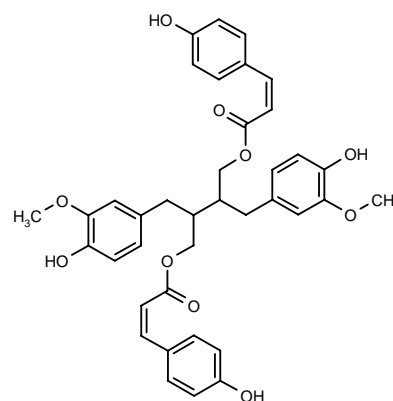


C₃₈ H₃₈ O₁₀; Mol wt: 654.7082

ACTION – Agent for the treatment of Alzheimer's disease isolated from a plant of the Vitaceae family, *Cayratia japonica* Gagn., whose activity was assessed by measuring its ability to inhibit β -amyloid 25-35-induced neurotoxicity in rat PC12 nerve cells (80.4% inhibition at 10 μM). Other compounds isolated from the same source are:



268375: C₃₈ H₃₈ O₁₀



268376: C₃₈ H₃₈ O₁₀

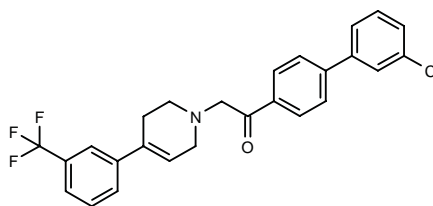
SOURCE – Wakamoto.

REFERENCES

1. Sonobe, T. et al. (Wakamoto Pharmaceutical Co., Ltd.) *Novel bioactive substance obtained from Cayratia japonica Gagn. belonging to Vitaceae family.* JP 98226668.

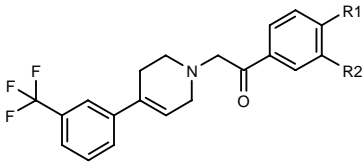
268916

1-(3'-Chlorobiphenyl-4-yl)-2-[4-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridin-1-yl]ethanone



C₂₆ H₂₁ Cl F₃ N O; Mol wt: 455.9049

ACTION – Neurotrophic and neuroprotective agent claimed for use in the symptomatic treatment of dementia of the Alzheimer's type, particularly in combination with other therapeutic agents such as acetylcholinesterase inhibitors, muscarinic M₁ receptor agonists, nicotinic agonists, NMDA antagonists and nootropics. Other specifically claimed benzoylalkyl-1,2,3,6-tetrahydropyridine derivatives include the following:



Compound	R1	R2	Formula
268917	2-Cl-Ph	H	C ₂₆ H ₂₁ ClF ₃ NO
268918	4-Cl-Ph	H	C ₂₆ H ₂₁ ClF ₃ NO
268919	i-Bu	H	C ₂₄ H ₂₆ F ₃ NO
268920	CH ₂ Ph	H	C ₂₇ H ₂₄ F ₃ NO
268921	cyclohexyl	H	C ₂₆ H ₂₆ F ₃ NO
268922	4-F-Ph	H	C ₂₆ H ₂₁ F ₄ NO
268923	Ph	H	C ₂₆ H ₂₂ F ₃ NO
268924	Bu	H	C ₂₄ H ₂₆ F ₃ NO
268925	t-Bu	H	C ₂₄ H ₂₆ F ₃ NO
268926	Et	Et	C ₂₄ H ₂₆ F ₃ NO
268927	2-CF ₃ -Ph	H	C ₂₇ H ₂₁ F ₆ NO
268928	3-CF ₃ -Ph	H	C ₂₇ H ₂₁ F ₆ NO
268929	4-CF ₃ -Ph	H	C ₂₇ H ₂₁ F ₆ NO

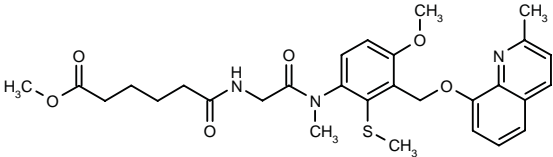
SOURCE – Sanofi.

REFERENCES

1. Baroni, M. et al. (Sanofi) *Use of benzoylalkyl-1,2,3,6-tetrahydropyridines*. WO 9828274.

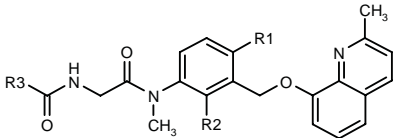
269077

5-[N-[N-[4-Methoxy-2-(methylsulfonyl)-3-(2-methyl-quinolin-8-yloxymethyl)phenyl]-N-methylcarbamoyl-methyl]carbamoyl]pentanoic acid methyl ester



C29 H35 N3 O6 S; Mol wt: 553.6765

ACTION – Bradykinin B₂ receptor antagonist, as demonstrated in a binding assay by a K_i value of 5.4 nM against [³H]-bradykinin binding in guinea pig ileum preparations. In a functional assay, compound was shown to antagonize bradykinin-induced contractions in guinea pig ileal strips with an IC₅₀ value of 56 nM. Claimed for the treatment or prevention of Alzheimer's disease and liver cirrhosis. Other compounds from this series of benzyloxy-substituted N-containing heterocyclic derivatives include the following:



Compound	R1	R2	R3	Formula
269078	Cl	CN	NHEt	C ₂₄ H ₂₄ ClN ₅ O ₃
269079	Cl	CN	NH(CH ₂) ₄ NH ₂	C ₃₀ H ₃₁ ClF ₆ N ₆ O ₇
269080	OMe	CN	NHEt	C ₂₅ H ₂₇ N ₅ O ₄
269081	CH ₂ SH	OMe	4-CF ₃ -PhCH=CH	C ₃₂ H ₃₀ F ₃ N ₃ O ₄ S
269082	CH ₂ SH	CH ₂ SH	6-(AcNH)-3-Pyr-CH=CH	C ₃₂ H ₃₃ N ₅ O ₄ S ₂

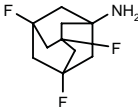
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Heitsch, H. et al. (Hoechst AG) *Fused N-heterocyclic cpds. substd. with benzyloxy, process for their preparation and their use as bradykinin receptor antagonists*. EP 867432, JP 98279563.

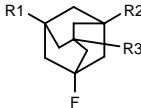
269497

3,5,7-Trifluoroadamantan-1-amine



C10 H14 F3 N; Mol wt: 205.2216

ACTION – Agent for the treatment of CNS disorders such as memory loss, Alzheimer's disease and Parkinson's disease, reported to enhance the release of neurotransmitters such as acetylcholine, dopamine and serotonin. It has improved metabolic stability compared to parent compounds in which the adamantane moiety is not fluorinated. Other specifically claimed fluoro-substituted adamantane derivatives include the following:



Compound	R1	R2	R3	Formula
269498	H	CO ₂ Me	OH	C ₁₂ H ₁₇ FO ₃
269499	F	NH ₂	H	C ₁₀ H ₁₅ F ₂ N
269500	F	CO ₂ Me	OH	C ₁₂ H ₁₆ F ₂ O ₃
269501	F	CO ₂ H	F	C ₁₁ H ₁₃ F ₃ O ₂

SOURCE – Pfizer.

REFERENCES

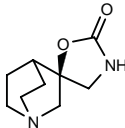
1. Jasys, V.J. and Volkmann, R.A. (Pfizer Inc.) *Fluoro-substd. adamantane derivs*. EP 870757, JP 98298135.

AR-R17779

267802

(S)-Spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin]-2'-one

AR-R13489 (as racemic)



C9 H14 N2 O2; Mol wt: 182.2216

ACTION – High-affinity, selective full agonist at the neuronal nicotinic acetylcholine receptor (nAChR) $\alpha 7$ subtype ($K_i = 91$ nM vs. 480 nM for (–)-nicotine against [125 I]- α -BTX binding in rat hippocampal membranes) with high selectivity relative to other nAChR subtypes, muscarinic M_1 and 5-HT $_3$ receptors. In a functional assay, it was more potent and efficacious than nicotine in eliciting current in oocytes expressing rat nAChR $\alpha 7$, but it was less potent and efficacious in oocytes expressing chick nAChR $\alpha 7$. In rat radial-maze tasks, the compound improved learning and reversed cognitive impairment induced by lesions of the septohippocampal projection. In behavioral tests in rats and mice, it exhibited moderate anxiolytic properties without signs of neuromuscular impairment or hyperlocomotion. Potentially useful for the treatment of cognitive disorders and anxiety.

SOURCE – Astra Arcus.

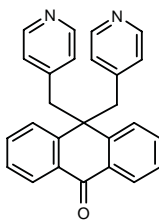
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XE-991

200999

10,10-Bis(4-pyridylmethyl)anthracen-10(9H)-one



C26 H20 N2 O; Mol wt: 376.4570

ACTION – Cognition-enhancing agent for the treatment of Alzheimer's disease, a linopirdine analog that acts by enhancing K $^+$ -evoked acetylcholine (ACh) release. It was about 10 times more potent than linopirdine in enhancing [3 H]-ACh release from rat hippocampal slices ($EC_{50} = 0.49$ μ M vs. 4.2 μ M). Compound was also able to increase the release of [3 H]-dopamine and [3 H]-D-aspartic acid from striatal and hippocampal slices, respectively, with EC_{50} values of 0.20 and 0.25 μ M, respectively. *In vivo*, at a dose of 5 mg/kg p.o. it increased hippocampal extracellular ACh by about 100% over baseline, whereas linopirdine had no significant effect at this dose. XE-991 appears to be more potent and selective than linopirdine for blocking the voltage-dependent K $^+$ current known as K_M .

SOURCE – DuPont Pharmaceuticals.

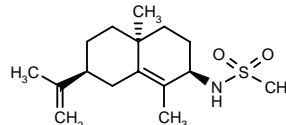
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TREATMENT OF CEREBROVASCULAR DISEASES

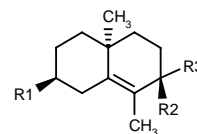
261183

(2*R*,4*a**S*,7*S*)-*N*-(7-Isopropenyl-1,4*a*-dimethyl-2,3,4,4*a*,5,6,7,8-octahydronaphthalen-2-yl)methanesulfonamide

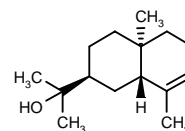


C16 H27 N O2 S; Mol wt: 297.4603

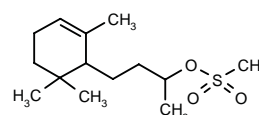
ACTION – P/Q-type calcium channel antagonist ($IC_{50} = 1.0$ μ M for inhibition 45 Ca $^{2+}$ influx in rat brain synaptosomes) with potential in the treatment of stroke, dementia, epilepsy, head injury, Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease, AIDS-related dementia and migraine. Other related compounds include the following:



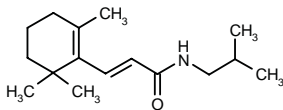
Compound	R1	R2	R3	Formula
266478	i-Pr	-O-		C $_{15}$ H $_{24}$ O
266479	C(Me)=CH2	NH2	H	C $_{15}$ H $_{25}$ N



266477: C15 H26 O



266480: C14 H26 O3 S



266481: C16 H27 N O

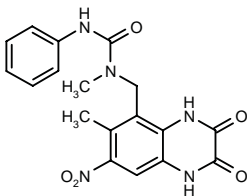
SOURCE – Shionogi.

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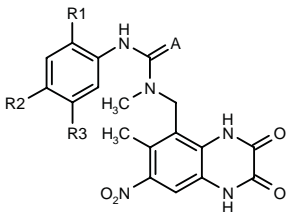
266182

N-Methyl-*N*-(6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)-*N*'-phenylurea



C18 H17 N5 O5; Mol wt: 383.3623

ACTION – Glutamate receptor antagonist acting at AMPA, kainate and, particularly, the glycine binding site of NMDA receptors (IC₅₀ = 0.13, 0.82 and 0.008 μM, respectively). Claimed for the treatment of stroke, cerebral hypoxia/ischemia, Alzheimer's disease, Parkinson's disease and Huntington's disease. Within this series of substituted quinoxaline-2,3-diones, the following are also included:



Compound	R1	R2	R3	A	Formula
266915	H	OMe	H	O	C ₁₉ H ₁₉ N ₅ O ₆
266916	H	OMe	H	S	C ₁₉ H ₁₉ N ₅ O ₅ S
266917	Me	Me	H	O	C ₂₀ H ₂₁ N ₅ O ₅
266918	OMe	H	OMe	O	C ₂₀ H ₂₁ N ₅ O ₇
266919	CF3	H	H	O	C ₁₉ H ₁₆ F ₃ N ₅ O ₅
266920	H	CO2Et	H	O	C ₂₁ H ₂₁ N ₅ O ₇

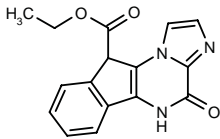
SOURCE – Warner-Lambert.

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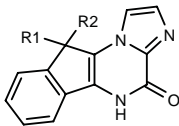
268738

4-Oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]-pyrazine-10-carboxylic acid ethyl ester



C16 H13 N3 O3; Mol wt: 295.2967

ACTION – Cerebral antiischemic and neuroprotective agent, an AMPA receptor antagonist that also acts as a noncompetitive glycine-site NMDA receptor antagonist. Within this series of specifically claimed imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one derivatives, the following are also included:



Compound	R1	R2	Formula
268738	CO2Et	H	C ₁₆ H ₁₃ N ₃ O ₃
268739	1-Me-2-imidazolyl-CH2	H	C ₁₈ H ₁₅ N ₅ O
268740	(R)-NHCOC(OMe)(Ph)CF3	H	C ₂₃ H ₁₇ F ₃ N ₄ O ₃
268741	NH2	Me	C ₁₄ H ₁₂ N ₄ O
268742	-CH(3-NH2-Ph)-		C ₂₀ H ₁₄ N ₄ O
268743	CH2CH2CO2H	NH2	C ₁₆ H ₁₄ N ₄ O ₃
268744	1-Me-5-imidazolyl-CH2	H	C ₁₈ H ₁₅ N ₅ O
268745	2-CO2H-1-pyrrolyl	H	C ₁₈ H ₁₂ N ₄ O ₃
268746	NH2	Bu	C ₁₇ H ₁₈ N ₄ O

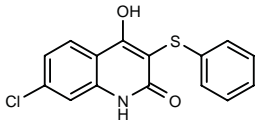
SOURCE – Rhône-Poulenc Rorer.

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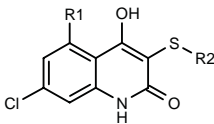
269005

7-Chloro-4-hydroxy-3-(phenylsulfanyl)quinolin-2(1*H*)-one



C15 H10 Cl N O2 S; Mol wt: 303.7680

ACTION – Potent and specific antagonist at the strychnine-insensitive glycine binding site on the NMDA receptor complex, reported to possess good CNS penetration and high solubility. Claimed for the treatment or prevention of ischemic, hypoxic or hypoglycemic CNS damage, neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, Parkinson's disease, epilepsy and stroke, as well as for use as an anticonvulsant, analgesic, antidepressant, anxiolytic and antipsychotic agent. A representative compound from a series of quinolinic sulfide derivatives, wherein the following are also included:



Compound	R1	R2	Formula
269006	H	3-Me-Ph	C ₁₆ H ₁₂ ClNO ₂ S
269007	H	3-Br-Ph	C ₁₅ H ₉ BrClNO ₂ S
269008	Cl	4-MeO-Ph	C ₁₆ H ₁₁ Cl ₂ NO ₃ S
269009	Cl	2-Br-Ph	C ₁₅ H ₈ BrCl ₂ NO ₂ S
269010	H	2-benzothiazolyl	C ₁₆ H ₉ ClN ₂ O ₂ S ₂
269011	Cl	3-CO ₂ H-2-Pyr	C ₁₅ H ₈ Cl ₂ N ₂ O ₄ S
269012	Cl	1,2,4-triazol-3-yl	C ₁₁ H ₆ Cl ₂ N ₄ O ₂ S
269013	H	4-(PhCH ₂ CONH)-Ph	C ₂₃ H ₁₇ ClN ₂ O ₃ S
269014	Cl	4-(3-Pyr-CONH)-Ph	C ₂₁ H ₁₃ Cl ₂ N ₃ O ₃ S
269015	Cl	4-(4-Cl-PhCH ₂ NH)-Ph	C ₂₂ H ₁₆ Cl ₄ N ₂ O ₂ S

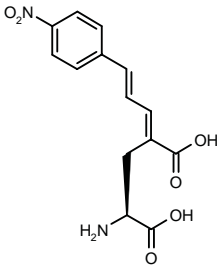
SOURCE – Korea Res. Inst. Chem. Technol., Taejon (KR).

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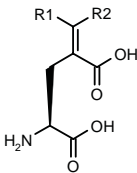
269083

(2*S,E,E*)-2-Amino-4-(4-nitrocinnamylidene)glutaric acid



C14 H14 N2 O6; Mol wt: 306.2726

ACTION – Neuroprotective agent, an ionotropic glutamate receptor agonist with selectivity for the GluR5 subtype (*K_i* < 1000 μM). Potentially useful for the treatment of neurodegenerative disorders such as stroke, cerebral ischemia, head and spinal cord trauma, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, AIDS-related dementia and Huntington’s chorea, and also as an antipsychotic, anticonvulsant, analgesic, antiemetic, anxiolytic and antidepressant. Other specifically claimed glutamic acid derivatives include the following:



Compound	R1	R2	Formula
269084	4-N(Me)2-PhCH=CH	H	C ₁₆ H ₂₀ N ₂ O ₄
269085	CH=CHPh	H	C ₁₄ H ₁₅ NO ₄
269086	Bu	H	C ₁₀ H ₁₇ NO ₄
269087	Me	Me	C ₈ H ₁₃ NO ₄
269088	-(CH ₂)3-		C ₉ H ₁₃ NO ₄
269089	4-Cl-Ph	H	C ₁₂ H ₁₂ ClNO ₄
269090	-(CH ₂)5-		C ₁₁ H ₁₇ NO ₄
269091	cyclopentyl	H	C ₁₁ H ₁₇ NO ₄
269092	-(CH ₂)4-		C ₁₀ H ₁₅ NO ₄

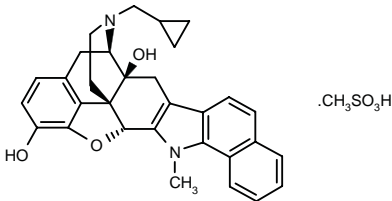
SOURCE – Lilly.

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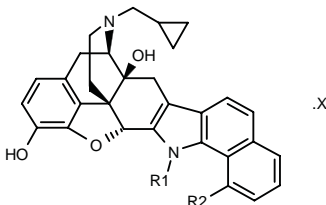
269145

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14β-dihydroxy-1'-methyl-6,7-didehydro-1'-*H*-benzo[6',7']indolo-[2',3':6,7]morphinan methanesulfonate

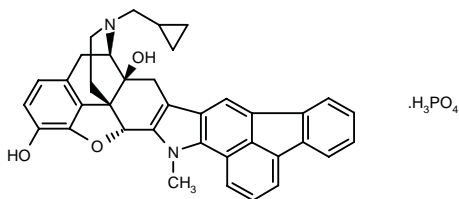


C31 H30 N2 O3 . C H4 O3 S; Mol wt: 574.6946

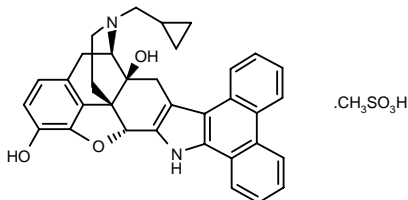
ACTION – Neuroprotective and cerebral antiischemic agent shown to exhibit potent protective effects against glutamate toxicity in cultured rat neurons (*ED*₅₀ = 0.026 μM). It also reduced infarct volume in a rat model of middle cerebral artery occlusion–reperfusion injury (85% at 3 mg/kg i.p.). Other representative compounds within this series of indolomorphinan derivatives include the following:



Compound	R1	R2	X	Formula
269146	H	H	HCl	C ₃₀ H ₂₈ N ₂ O ₃ .HCl
269147	H	Cl	MeSO ₃ H	C ₃₀ H ₂₇ ClN ₂ O ₃ .CH ₄ O ₃ S
269148	CH ₂ Ph	H	MeSO ₃ H	C ₃₇ H ₃₄ N ₂ O ₃ .CH ₄ O ₃ S



269149: C37 H32 N2 O3 . H3 P O4



270164: C34 H30 N2 O3 . C H4 O3 S

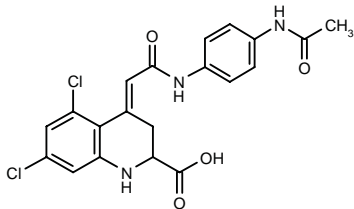
SOURCE – Toray.

REFERENCES

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269215

(+)-(E)-4-[N-(4-Acetamidophenyl)carbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid



C20 H17 Cl2 N3 O4; Mol wt: 434.2773

ACTION – The (+)-enantiomer of a known compound* found to be a potent and selective antagonist at the strychnine-insensitive glycine binding site on the NMDA receptor complex (pK_i = 8.8) and reported to inhibit NMDA-induced convulsions in mice and to provide neuroprotection in a murine model of middle cerebral artery occlusion.

SOURCE – Glaxo Wellcome.

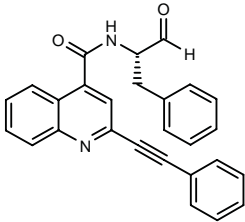
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*See **251158** Drug Data Report 1997, 019(07): 0606.

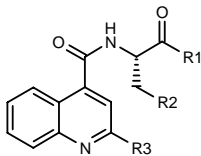
269216

N-[2-(Phenylethynyl)quinolin-4-ylcarbonyl]-L-phenylalaninal



C27 H20 N2 O2; Mol wt: 404.4670

ACTION – Agent for the treatment of neurodegenerative disorders, stroke and brain injury, an inhibitor of calpain. Within this series of quinoline and naphthalene carboxamide derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269217	H	Ph	Ph	C ₂₅ H ₂₀ N ₂ O ₂
269218	H	Ph	4-Cl-Ph	C ₂₅ H ₁₉ ClN ₂ O ₂
269219	H	Ph	4-Ph-Ph	C ₃₁ H ₂₄ N ₂ O ₂
269220	H	Ph	1-adamantyl	C ₂₉ H ₃₀ N ₂ O ₂
269221	H	Ph	4-PhO-Ph	C ₃₁ H ₂₄ N ₂ O ₃
269222	H	Ph	2-Ph-Ph	C ₃₁ H ₂₄ N ₂ O ₂
269223	H	Ph	2-Pyr-ethynyl	C ₂₆ H ₁₉ N ₃ O ₂
269224	H	Ph	4-Ph-1-Piz	C ₂₉ H ₂₈ N ₄ O ₂
269225	H	Ph	4-(3-Pyr)-Ph	C ₃₀ H ₂₃ N ₃ O ₂
269226	H	(CH ₂) ₃ -NHSO ₂ Ph	Ph	C ₂₈ H ₂₇ N ₃ O ₄ S
269227	H	4-Pyr-CH ₂ O-CONH(CH ₂) ₃	Ph	C ₂₉ H ₂₈ N ₄ O ₄
269228	CONHBu	Ph	Ph-ethynyl	C ₃₂ H ₂₉ N ₃ O ₃

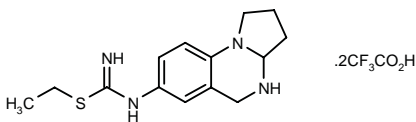
SOURCES – Cephalon; SmithKline Beecham.

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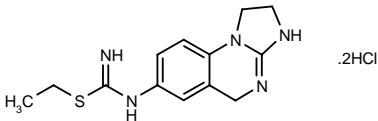
269431

S-Ethyl-N-(1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazolin-7-yl)isothiourea bis(trifluoroacetate)



C14 H20 N4 S . 2 C2 H F3 O2; Mol wt: 504.4498

ACTION – An inhibitor of nitric oxide synthase (NOS) with selectivity for the neuronal isoform (nNOS; IC₅₀ = 13.7 nM) over the endothelial (eNOS; IC₅₀ = 1082.3 nM) and the inducible isoforms (iNOS; IC₅₀ = 11,193.4 nM), potentially useful for the treatment of cerebrovascular disorders, head injury, spinal cord injury, pain, Parkinson’s disease, Alzheimer’s disease, convulsions, rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes. Another hetero-tricyclic compound is:



269432: C13 H17 N5 S . 2HCl

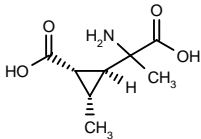
SOURCE – Chugai.

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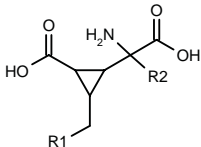
269474

(1’R*,2’R*,3’R*)-2-Amino-2-(2-carboxy-3-methylcyclopropyl)propionic acid



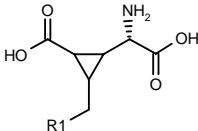
C8 H13 N O4; Mol wt: 187.1937

ACTION – Neuronal injury inhibitor with affinity for metabotropic glutamate receptors, as demonstrated by the selective displacement of 1S,3R-ACPD-sensitive [³H]-glutamate binding in rat brain cell membranes. Preferred compounds have agonist activity. Potentially useful for the treatment of neurological and CNS disorders such as stroke, cerebral ischemia, spinal cord and head trauma, Alzheimer’s disease, amyotrophic lateral sclerosis and Parkinson’s disease. Other specifically claimed cyclopropyl glycine derivatives include the following:



Compound	R1	R2	Isomer	Formula
269475	H	CH2CH2Ph	1’R*,2’R*,3’R*	C16H19NO4
269476	CH2Ph	CH2CH2Ph	1’R*,2’R*,3’R*	C22H25NO4
269477	Bu	CH2CH2Ph	1’R*,2’R*,3’R*	C19H27NO4
269478	C8H17	CH2CH2Ph	1’R*,2’R*,3’R*	C23H35NO4
269479	C8H17	CH2CH2Ph	1’R*,2’S*,3’S*	C23H35NO4
269480	H	9-xanthyl-CH2	1’R*,2’R*,3’R*	C13H15N5O6
269481	Me	9-xanthyl-CH2	1’R*,2’R*,3’R*	C14H17N5O6

Compound	R1	R2	Isomer	Formula
269482	Et	9-xanthyl-CH2	1’R*,2’R*,3’R*	C15H19N5O6
269483	Pr	9-xanthyl-CH2	1’R*,2’R*,3’R*	C16H21N5O6
269484	Bu	9-xanthyl-CH2	1’R*,2’R*,3’R*	C17H23N5O6
269485	C5H11	9-xanthyl-CH2	1’R*,2’R*,3’R*	C18H25N5O6
269486	C8H17	9-xanthyl-CH2	1’R*,2’R*,3’R*	C21H29N5O6
269487	CH2Ph	9-xanthyl-CH2	1’R*,2’R*,3’R*	C20H21N5O6
269488	i-Pr	9-xanthyl-CH2	1’R*,2’R*,3’R*	C16H21N5O6



Compound	R1	Isomer	Formula
269489	H	1’R,2’R,3’R	C7H11NO4
269490	H	1’S,2’S,3’S	C7H11NO4
269491	Me	1’R,2’R,3’R	C8H13NO4
269492	Me	1’S,2’S,3’S	C8H13NO4
269493	Et	1’R,2’R,3’R	C9H15NO4
269494	Et	1’S,2’S,3’S	C9H15NO4

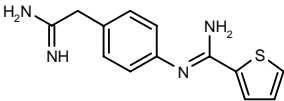
SOURCE – Lilly.

REFERENCES

1. Pedregal Tercero, C. et al. (Lilly SA) *Cyclopropylglycine derivs. with pharmaceutical properties*. EP 870760, JP 98287633.

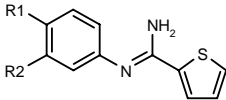
269712

N²-[4-(Amidinomethyl)phenyl]thiophene-2-carboxamidine



C13 H14 N4 S; Mol wt: 258.3476

ACTION – An inhibitor of neuronal nitric oxide synthase (nNOS), giving IC₅₀ values of 0.06 and 0.068 μM, respectively, against enzyme from rat brain tissue and human recombinant nNOS expressed in CHO-K1 cells. Within this series of amidino derivatives, the following are also included:

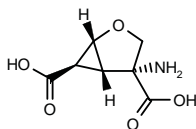


Compound	R1	R2	Formula
269713	1-imidazolyl-CH2CH2	H	C16H16N4S
269714	1-imidazolyl-CH2	H	C15H14N4S
269715	H	1-imidazolyl-CH2	C15H14N4S
269716	2-benzimidazolyl-NH	H	C18H15N5S

SOURCE – Mitsui Chemicals.

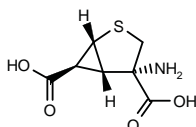
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1. Ando, T. et al. (Mitsui Chemicals, Inc.) *Novel amidine derivs. having NO synthetase inhibitory effect*. JP 98265450.

LY-379268*1-13**252374****(1*R*,4*R*,5*S*,6*R*)-4-Amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid**

C7 H9 N O5; Mol wt: 187.1501

ACTION – Neuroprotective agent, a potent and selective group 2 metabotropic glutamate receptor (mGluR) agonist that displays high affinity for recombinant mGluR2 and mGluR3 ($K_i = 16.1$ and 5.60 nM, respectively) and potent agonist activity for suppressing forskolin-stimulated cAMP accumulation in RGT cells expressing mGluR2 ($EC_{50} = 0.32$ nM) and mGluR3 ($EC_{50} = 0.15$ nM); lower affinity and less potent agonist activity were noted for mGluR8 ($K_i = 5872$ nM; $EC_{50} = 1690$ nM). *In vitro*, it protected rat cortical neuronal cell cultures from both NMDA- and kainate-induced excitotoxicity. Studies in rats demonstrated that it is a potent, orally and systemically active compound that penetrates well into the CNS. *In vivo*, it dose-dependently reduced kainate neurotoxicity in rats at doses of 3, 10 and 30 mg/kg i.p. 1 h before kainate, and it displayed good neuroprotective effect in a gerbil model of global cerebral ischemia, with 88% protection against CA1 damage following a dose of 10 mg/kg i.p. given at 30 min after occlusion. Further studies in rats indicated that the compound may also be useful for the treatment of pain. Another related compound is:

**LY-389795**2,3,8 [252860]:** C7 H9 N O4 S**SOURCE** – Lilly.**REFERENCES**

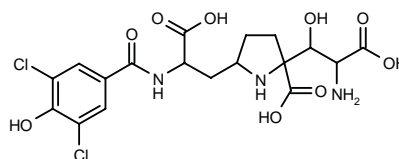
- Levine, L.R. (Eli Lilly and Company) *Treatment for premenstrual dysphoric disorder*. WO 9832436.
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- Jordan, W.H. et al. *Kainate neurotoxicity in Fischer 344 rats is inhibited by the mGluR2/3 agonist LY379268*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.5.
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- Lam, A.G.M. et al. *Effects of the selective group II metabotropic glutamate receptor agonist LY379268 on energy metabolism in the rat brain*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.4.
- Lodge, D. et al. *LY379268 is an orally active metabotropic glutamate receptor agonist: Electrophysiological studies in vivo*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.3.
- Massey, S.M. et al. *Synthesis and pharmacological characterization of heterobicyclic amino acids as potent and selective group II metabotropic glutamate receptor agonists*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 119.
- Monn, J.A. et al. *In vitro characterization of LY379268: A highly potent and selective agonist for group II metabotropic glutamate receptors*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.1.

10. O'Neill, M.J. et al. *Neuroprotective effects of a novel systemically active mGlu2/3 receptor agonist LY379268 in global cerebral ischaemia*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.6.

11. Sharpe, E.F. et al. *Effects of the selective group II mGluR agonist, LY379268, on carrageenan-induced hyperalgesia*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.7.

12. Simmons, R.M.A. et al. *LY379268, a novel mGlu2/3 receptor agonist, mediates nociceptive responses in vivo in rats*. Soc Neurosci Abst 1998, 24(Part 1): Abst 232.8.

13. Valli, M.J. et al. *Asymmetric synthesis and neuroprotective properties of 1*R*,4*R*,5*S*,6*R*-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylate (LY379268): A novel subtype selective metabotropic glutamate receptor*. 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 120.

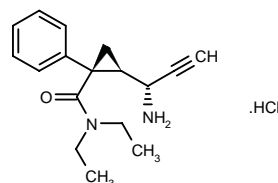
*Identified compound **252374** Drug Data Report 1997, 019(09): 0785.**Identified compound **252860** (see **252374**) Drug Data Report 1997, 019(09): 0785.**PF-1191****269314****2-Amino-3-[2-carboxy-5-[2-carboxy-2-(3,5-dichloro-4-hydroxybenzamido)ethyl]pyrrolidin-2-yl]-3-hydroxypropionic acid**

C18 H21 Cl2 N3 O9; Mol wt: 494.2819

ACTION – Neuroprotective agent isolated from a culture of *Eupenicillium shearii* PF-1191 (FERM BP-6263) that inhibits kainic acid-induced neurotoxicity, as demonstrated in primary cultured rat hippocampal cells ($IC_{50} = 0.45$ μ M).

SOURCE – Meiji Seika.**REFERENCES**

- Seto, H. et al. (Meiji Seika Kaisha, Ltd.) *Physiologically active substance PF1191 and process for producing the same*. WO 9841503.

PPYDC**268118****(1*S*,2*R*)-2-[1(*R*)-Amino-2-propynyl]-*N,N*-diethyl-1-phenylcyclopropanecarboxamide hydrochloride**

C17 H22 N2 O . HCl; Mol wt: 306.8347

White crystals, m.p. 96-100 °C, $[\alpha]_D^{21} +73.1^\circ$ (c 0.840, CHCl3).

ACTION – Potent NMDA receptor antagonist ($IC_{50} = 0.29 \mu M$ against [3H]-MK-801 binding in rat cerebral cortical synaptic membranes), a milnacipran analog proven to act as an open channel blocker in *Xenopus* oocytes. Its pharmacological effects on NMDA receptors are different from those of known blockers such as MK-801, especially as regards its shorter recovery time constant. It also showed potent 5-HT reuptake-inhibitory activity ($K_i = 0.19 \mu M$), although it was much less potent than milnacipran. Potentially useful for the treatment of acute and chronic neurodegenerative disorders such as epilepsy and stroke.

SOURCES – Hokkaido University, Sapporo (JP); Kyushu Institute of Technology, Iizuka (JP).

REFERENCES

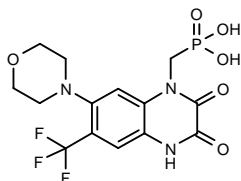
1. Shuto, S. et al. *Synthesis and biological activity of conformationally restricted analogues of milnacipran: (1S,2R)-1-Phenyl-2-[(R)-1-amino-2-propynyl]-N,N-diethyl-cyclopropanecarboxamide is a novel class of NMDA receptor channel blocker.* J Med Chem 1998, 41(18): 3507.

ZK-200775

261891

7-Morpholino-2,3-dioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxalin-1-ylmethylphosphonic acid

MPQX



C₁₄ H₁₅ F₃ N₃ O₆ P; Mol wt: 409.2555

ACTION – Competitive, high-affinity AMPA/kainate receptor antagonist ($IC_{50} = 120$ and 32 nM, respectively, against [3H]-AMPA and [3H]-CNQX binding in rat cortical membranes) with little or no affinity for NMDA channel-associated binding sites. Compound showed neuroprotective activity and a wide therapeutic window in rodent models of ischemia and head trauma; it protected rat brain from damage induced by permanent or transient focal cerebral ischemia when treatment was delayed for up to 5 h after occlusion or 2 h after the onset of reperfusion. Compound was devoid of renal toxicity and showed minimal systemic side effects at effective doses. Its broad-spectrum neuroprotective activity, wide therapeutic window and favorable safety profile suggest it may be an excellent candidate for therapeutic intervention in stroke.

SOURCES – Novo Nordisk; Schering AG.

REFERENCES

1. Huth, A. and Turski, L. (Schering AG) *Quinoxalindione derivs., their preparation and their use in drugs.* DE 4314591, DE 4344486, EP 696288, JP 96508037, US 5750525, WO 9425469.

2. Huth, A. et al. (Schering AG) *New quinoxalindione derivs., their preparation and use in medicaments.* DE 19545251, EP 876357, WO 9719066.

3. Rudd, J.A. et al. *The anti-emetic potential of ZK 200.775 in the ferret and Suncus murinus: Role of the AMPA receptor.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 40.40.

4. Turski, L. et al. *Neuroprotection by MPQX, a competitive non-NMDA glutamate receptor antagonist, against experimental ischemia and head trauma.* Soc Neurosci Abst 1997, 23(Part 2): Abst 946.18.

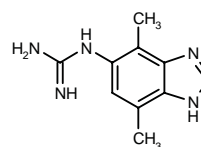
5. Turski, L. et al. *ZK200775: A phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma.* Proc Natl Acad Sci USA 1998, 95(18): 10960.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

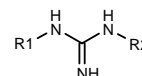
266181

N-(4,7-Dimethylbenzimidazol-5-yl)guanidine



C₁₀ H₁₃ N₅; Mol wt: 203.2477

ACTION – α_2 -Adrenoceptor agonist preferably for use in the treatment of nasal congestion, reported to be devoid of side effects. Also useful for the treatment or prevention of otitis media, sinusitis, asthma, cough, chronic obstructive pulmonary disease, benign prostatic hypertrophy, cardiovascular disorders, glaucoma, conjunctivitis, gastrointestinal disorders, migraine, pain and substance abuse or withdrawal. Within this series of guanidyl heterocycle derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
266894	H	2,4-(Me)2-5-benzimidazolyl	C ₁₀ H ₁₃ N ₅
266895	H	1,4-(Me)2-5-benzimidazolyl	C ₁₀ H ₁₃ N ₅
266896	H	4-Br-5-benzimidazolyl	C ₈ H ₆ BrN ₅
266897	Me	4-Me-5-benzimidazolyl	C ₁₀ H ₁₃ N ₅
266898	H	8-Me-7-quinolyl	C ₁₁ H ₁₂ N ₄
266899	H	8-Br-7-quinolyl	C ₁₀ H ₉ BrN ₄
266900	H	6-Me-5-benzothiazolyl	C ₉ H ₁₀ N ₄ S
266901	H	4-Br-5-benzothiazolyl	C ₈ H ₇ BrN ₄ S
266902	H	4-Me-5-benzothiazolyl	C ₉ H ₁₀ N ₄ S

SOURCE – Procter & Gamble.

REFERENCES

1. Cupps, T.L. et al. (The Procter & Gamble Co.) *Guanidinyll heterocycle cpds. useful as α_2 -adrenoceptor agonists.* WO 9823596.

ACTION – Potent NMDA receptor antagonist ($IC_{50} = 0.29 \mu M$ against [3H]-MK-801 binding in rat cerebral cortical synaptic membranes), a milnacipran analog proven to act as an open channel blocker in *Xenopus* oocytes. Its pharmacological effects on NMDA receptors are different from those of known blockers such as MK-801, especially as regards its shorter recovery time constant. It also showed potent 5-HT reuptake-inhibitory activity ($K_i = 0.19 \mu M$), although it was much less potent than milnacipran. Potentially useful for the treatment of acute and chronic neurodegenerative disorders such as epilepsy and stroke.

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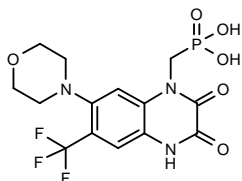
1. Shuto, S. et al. *Synthesis and biological activity of conformationally restricted analogues of milnacipran: (1S,2R)-1-Phenyl-2-[(R)-1-amino-2-propynyl]-N,N-diethyl-cyclopropanecarboxamide is a novel class of NMDA receptor channel blocker.* J Med Chem 1998, 41(18): 3507.

ZK-200775

261891

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MPQX



C₁₄ H₁₅ F₃ N₃ O₆ P; Mol wt: 409.2555

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3. Rudd, J.A. et al. *The anti-emetic potential of ZK 200.775 in the ferret and Suncus murinus: Role of the AMPA receptor.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 40.40.

4. Turski, L. et al. *Neuroprotection by MPQX, a competitive non-NMDA glutamate receptor antagonist, against experimental ischemia and head trauma.* Soc Neurosci Abst 1997, 23(Part 2): Abst 946.18.

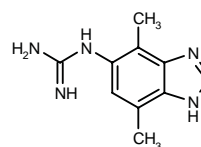
5. Turski, L. et al. *ZK200775: A phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma.* Proc Natl Acad Sci USA 1998, 95(18): 10960.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

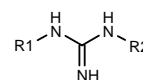
266181

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Compound	R1	R2	Formula
266894	H	2,4-(Me)2-5-benzimidazolyl	C ₁₀ H ₁₃ N ₅
266895	H	1,4-(Me)2-5-benzimidazolyl	C ₁₀ H ₁₃ N ₅
266896	H	4-Br-5-benzimidazolyl	C ₈ H ₆ BrN ₅
266897	Me	4-Me-5-benzimidazolyl	C ₁₀ H ₁₃ N ₅
266898	H	8-Me-7-quinolyl	C ₁₁ H ₁₂ N ₄
266899	H	8-Br-7-quinolyl	C ₁₀ H ₉ BrN ₄
266900	H	6-Me-5-benzothiazolyl	C ₉ H ₁₀ N ₄ S
266901	H	4-Br-5-benzothiazolyl	C ₈ H ₇ BrN ₄ S
266902	H	4-Me-5-benzothiazolyl	C ₉ H ₁₀ N ₄ S

SOURCE – Procter & Gamble.

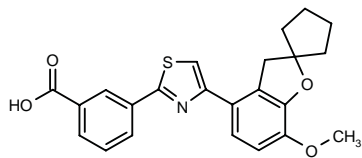
REFERENCES

1. Cupps, T.L. et al. (The Procter & Gamble Co.) *Guanidiny heterocycle cpds. useful as α_2 -adrenoceptor agonists.* WO 9823596.

ASTHMA THERAPY

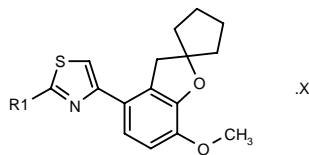
265491

3-[4-(7-Methoxyspiro[benzofuran-2(3*H*),1'-cyclopentan]-4-yl)thiazol-2-yl]benzoic acid



C23 H21 N O4 S; Mol wt: 407.4879

ACTION – Antiasthmatic and antiinflammatory agent, an inhibitor of phosphodiesterase type 4 (PDE4; –log IC₅₀ = 7.79). A representative compound from a series of 4-(2,3-dihydrobenzofuranyl)thiazoles, wherein the following are also included:



Compound	R1	X	Formula
266665	3-Pyr		C ₂₁ H ₂₀ N ₂ O ₂ S
266666	4-Pyr		C ₂₁ H ₂₀ N ₂ O ₂ S
266667	2-(EtOCO)-4-Pyr		C ₂₄ H ₂₄ N ₂ O ₄ S
266668	2-CO ₂ H-4-Pyr	1/2HCl	C ₂₂ H ₂₀ N ₂ O ₄ S.1/2HCl

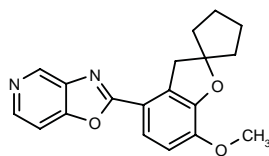
SOURCE – Byk Gulden.

REFERENCES

1. Amschler, H. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) (2,3-Dihydrobenzofuranyl)-thiazoles as phosphodiesterase inhibitors. WO 9821207.

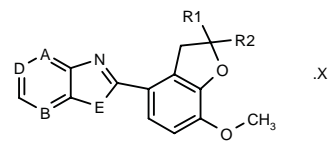
265493

2-(7-Methoxyspiro[benzofuran-2(3*H*),1'-cyclopentan]-4-yl)oxazolo[4,5-*c*]pyridine



C19 H18 N2 O3; Mol wt: 322.3622

ACTION – Antiasthmatic and antiinflammatory agent, an inhibitor of phosphodiesterase type 4 (PDE4; –log IC₅₀ = 8.76). A representative compound from a series of imidazo- and oxazolopyridines, wherein the following are also included:



Compound	R1,R2	A	B	D	E	X	Formula
266623	-(CH2)4-	N	CH	CH	O		C ₁₉ H ₁₈ N ₂ O ₃
266624	-(CH2)4-	CH	N	CH	O		C ₁₉ H ₁₈ N ₂ O ₃
266625	-(CH2)4-	CH	CH	N	NH		C ₁₉ H ₁₉ N ₃ O ₂
266626	-(CH2)5-	CH	CH	N	NH		C ₂₀ H ₂₁ N ₃ O ₂
266627	-(CH2)5-	N	CH	CH	NH	2HCl .1/2H ₂ O	C ₂₀ H ₂₁ N ₃ O ₂ .2HCl.1/2H ₂ O
266628	-(CH2)4-	C(Cl)	CH	N	NH		C ₁₉ H ₁₈ ClN ₃ O ₂

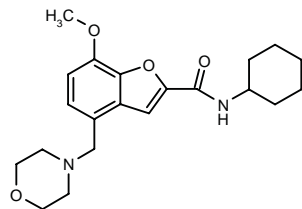
SOURCE – Byk Gulden.

REFERENCES

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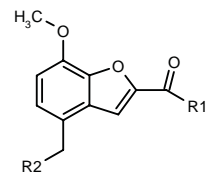
265518

N-Cyclohexyl-7-methoxy-4-(4-morpholinylmethyl)-benzofuran-2-carboxamide



C21 H28 N2 O4; Mol wt: 372.4622

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4) with potential in the treatment of inflammatory and allergic disorders such as asthma and allergic rhinitis, nephritis, autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, Crohn's disease and systemic lupus erythematosus, CNS disorders such as depression, amnesia and dementia, ischemia–reperfusion disorders, AIDS and in wound healing. A representative compound from a series of benzofuran derivatives, wherein the following are also included:



Compound	R1	R2	Formula
268145	cyclohexyl-NH	NHMe	C ₁₈ H ₂₄ N ₂ O ₃
268146	cyclohexyl-NH	cyclooctyl-NH	C ₂₈ H ₃₆ N ₂ O ₃
268147	cyclohexyl-NH	4-morpholinyl- -CH2CH2NH	C ₂₃ H ₃₃ N ₃ O ₄
268148	NHPh	NHMe	C ₁₈ H ₁₈ N ₂ O ₃
268149	NHPh	4-Me-1-Piz	C ₂₂ H ₂₆ N ₃ O ₃
268150	NHPh	4-morpholinyl- -CH2CH2NH	C ₂₃ H ₂₇ N ₃ O ₄

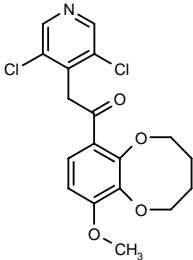
SOURCE – Kyowa Hakko.

REFERENCES

1. Ohshima, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Benzofuran derivs.* WO 9822452.

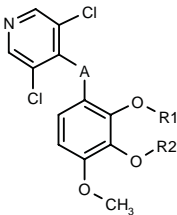
265520

2-(3,5-Dichloropyridin-4-yl)-1-(10-methoxy-2,3,4,5-tetrahydro-1,6-benzodioxocin-7-yl)ethanone

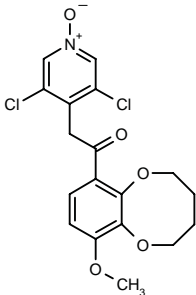


C18 H17 Cl2 N O4; Mol wt: 382.2413

ACTION – An inhibitor of phosphodiesterase type 4 (PDE4; 92% inhibition at 0.1 μM using human enzyme) with potential in the treatment of inflammatory and allergic disorders such as asthma and allergic rhinitis, nephritis, autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, Crohn’s disease and systemic lupus erythematosus, CNS disorders such as depression, amnesia and dementia, ischemia–reperfusion disorders, AIDS and in wound healing. Other compounds from this series of oxygen-containing heterocyclic derivatives include the following:



Compound	R1,R2	A	Formula
266466	-(CH2)2-	-CH2CO-	C ₁₆ H ₁₃ Cl ₂ NO ₄
266467	-(CH2)2-	-NHCO-	C ₁₅ H ₁₂ Cl ₂ N ₂ O ₄
266468	-(CH2)3-	-CH2CO-	C ₁₇ H ₁₅ Cl ₂ NO ₄
266469	-(CH2)3-	(E)-CH=CH-	C ₁₇ H ₁₅ Cl ₂ NO ₃



266470: C18 H17 Cl2 N O5

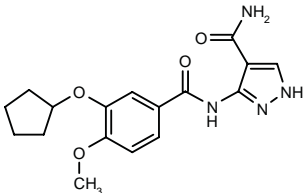
SOURCE – Kyowa Hakko.

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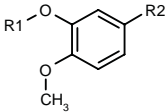
266198

3-(3-Cyclopentyloxy-4-methoxybenzamido)-1H-pyrazole-4-carboxamide



C17 H20 N4 O4; Mol wt: 344.3690

ACTION – Antiasthmatic agent, a phosphodiesterase inhibitor with some selectivity for PDE4, proven active in a rat passive cutaneous anaphylaxis (PCA) model following oral administration. Other specifically claimed compounds from this series of catechol derivatives include the following:



Compound	R1	R2	Formula
267184	cyclopentyl	5-(CONH2)- -4-imidazolyl-NHCO	C ₁₇ H ₂₀ N ₄ O ₄
267185	cyclopentyl	2-(CONH2)-3-thienyl-NHCO	C ₁₈ H ₂₀ N ₂ O ₄ S
267186	cyclopentyl	4-oxo-3H-thieno- [3,2-d]pyrimidin-2-yl	C ₁₈ H ₁₈ N ₂ O ₃ S
267187	cyclopentyl	6-oxo-6,7-dihydro- -1H-purin-2-yl	C ₁₇ H ₁₈ N ₄ O ₃
267188	cyclopentyl	7-oxo-6,7-dihydro-1H- -pyrazolo[4,3-d]pyrimidin-2-yl	C ₁₇ H ₁₈ N ₄ O ₃
267189	cyclopentyl	4-oxo-3,4-dihydro- -2-quinazoliny	C ₂₀ H ₂₀ N ₂ O ₃
267190	Me	4-oxo-3,4-dihydro- -2-quinazoliny	C ₁₆ H ₁₄ N ₂ O ₃

SOURCE – Cheil Jedang.

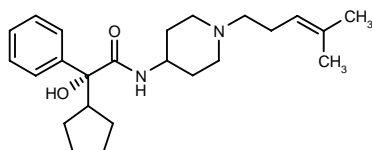
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J-104129

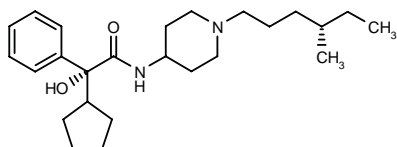
267753

2(*R*)-Cyclopentyl-2-hydroxy-*N*-[1-(4-methyl-3-pentenyl)-4-piperidinyl]-2-phenylacetamide



C24 H36 N2 O2; Mol wt: 384.5604

ACTION – Potent muscarinic M_3 receptor antagonist with high affinity ($K_i = 3.1$ nM) and selectivity ($M_2/M_3 = 110$) for this receptor. Compound exhibited good bronchodilating activity in rats, as determined by inhibition of acetylcholine-induced bronchoconstriction ($ID_{50} = 12$ μ g/kg i.v.), and good selectivity for bronchus relative to salivary gland ($ID_{50} = 110$ μ g/kg i.v. for inhibition of carbachol-induced salivary secretion) and heart ($ID_{50} > 3000$ μ g/kg i.v. for inhibition of acetylcholine-induced bradycardia); it did not inhibit oxotremorine-induced tremor, indicating low brain penetration. Potentially useful for the treatment of asthma, chronic obstructive pulmonary disease (COPD), urinary incontinence and irritable bowel syndrome. Another 4-acetamidopiperidine with a similar profile is:



J-106366 [267700]: C25 H40 N2 O2

SOURCE – Banyu.

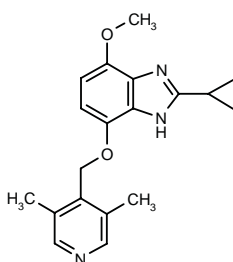
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3. Yamakawa, T. et al. *Synthesis and structure-activity-relationships of 4-acetamidopiperidines as M3 selective antagonists.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.294.

RPR-132703*

260131

2-Cyclopropyl-7-(3,5-dimethylpyridin-4-ylmethoxy)-4-methoxy-1*H*-benzimidazole



C19 H21 N3 O2; Mol wt: 323.3939

ACTION – Inhibitor of phosphodiesterase type 4 (PDE4) reported to have good selectivity (4-8-fold) for the low-affinity rolipram binding site and excellent *in vivo* efficacy. Potentially useful in the treatment of inflammatory disorders, especially asthma and rheumatoid arthritis.

SOURCE – Rhône-Poulenc Rorer.

REFERENCES

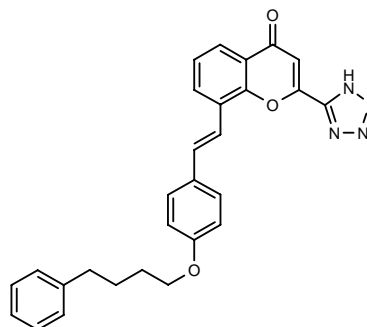
1. Cox, P.J. et al. (Rhône-Poulenc Rorer SA) *Subst. azabicyclic cpds. and their use as inhibitors of the production of TNF and cyclic AMP phosphodiesterase.* WO 9748697.
2. Aldous, D. et al. *Biological activity and side effect profile of RPR 132294 and RPR 132703 - Novel PDE4 inhibitors.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.337.

*Identified compound **260131** Drug Data Report 1998, 020(04): 0305.

LM-1484

267799

(*E*)-8-[2-[4-(4-Phenylbutoxy)phenyl]vinyl]-2-(1*H*-tetrazol-5-yl)-4*H*-benzopyran-4-one



C28 H24 N4 O3; Mol wt: 464.5226

ACTION – Antiasthmatic agent, the most potent LTD₄ (CysLT₁) antagonist from a series of stilbene derivatives. The pranlukast analog showed high potency in binding studies ($K_i = 0.47 \pm 0.29$ nM for inhibition of [³H]-LTD₄ binding in guinea pig lung membranes) and in the guinea pig model of LTD₄-induced bronchoconstriction ($ID_{50} = 0.3$ μ mol/kg p.o.). This compound and its tromethamine salt displayed improved oral bioavailability in mice compared to pranlukast, giving a 17- and 29-fold increase, respectively, in AUC after a single dose.

SOURCE – Menarini.

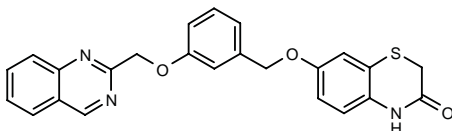
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VUF-K-8707

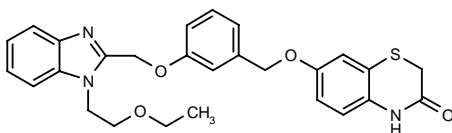
267683

7-[3-(Quinazolin-2-ylmethoxy)benzyloxy]-2*H*-1,4-benzothiazin-3(4*H*)-one



C₂₄ H₁₉ N₃ O₃ S; Mol wt: 429.4981

ACTION – Agent for the treatment of allergic disorders, especially bronchial asthma, that acts as a potent LTD₄ (CysLT₁) receptor antagonist ($K_D = 9.7$ nM against [³H]-LTD₄ binding in guinea pig lung membranes). The related compound **VUF-K-9015** displayed less potent LTD₄ antagonist activity but was also active as a histamine H₁ receptor antagonist ($K_D = 8.67$ μM).



VUF-K-9015 [267684]: C₂₇ H₂₇ N₃ O₄ S

SOURCES – Kowa; Vrije Universiteit, Amsterdam (NL).

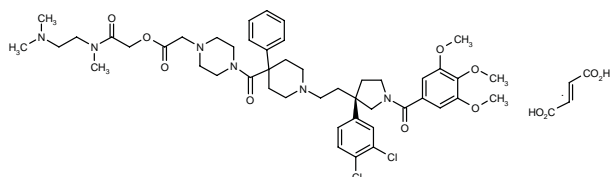
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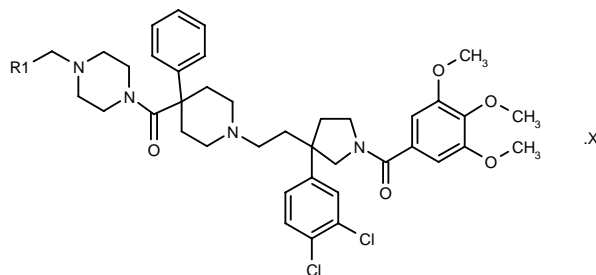
268640

2-[4-[1-[2-[3(*R*)-(3,4-Dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidin-3-yl]ethyl]-4-phenylpiperidin-4-ylcarbonyl]piperazin-1-yl]acetic acid *N*-[2-(dimethylamino)-ethyl]-*N*-methylcarbamoylmethyl ester fumarate

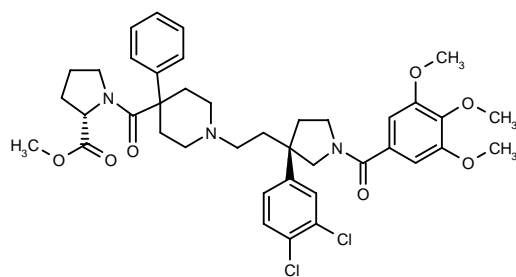


C₄₇ H₆₂ Cl₂ N₆ O₈ . C₄ H₄ O₄; Mol wt: 1026.0180

ACTION – Tachykinin receptor antagonist with high affinity for NK₁ (IC₅₀ = 2.09 nM) and NK₂ receptors (IC₅₀ = 0.90 nM), claimed for the treatment of asthma, cough and bronchitis. Within this series of carboxy substituted cyclic carboxamides, the following are also included:



Compound	R1	Isomer	X	Formula
268641	CO ₂ H	S	HCl	C ₄₀ H ₄₆ Cl ₂ N ₄ O ₇ .HCl
268643	CH ₂ CH ₂ CO ₂ H	R	HCl	C ₄₂ H ₅₂ Cl ₂ N ₄ O ₇ .HCl
268644	CO ₂ CH ₂ CON(Et) ₂	R	fumarate	C ₄₆ H ₅₉ Cl ₂ N ₅ O ₈ .C ₄ H ₄ O ₄
268645	CO ₂ CH ₂ CO-N(CH ₂ CH ₂ OH) ₂	R	fumarate	C ₄₆ H ₅₉ Cl ₂ N ₅ O ₁₀ .C ₄ H ₄ O ₄



268642: C₄₀ H₄₇ Cl₂ N₃ O₇

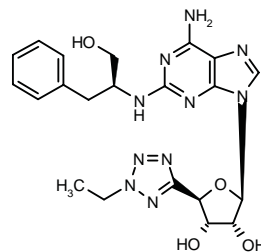
SOURCE – Hoechst Marion Roussel.

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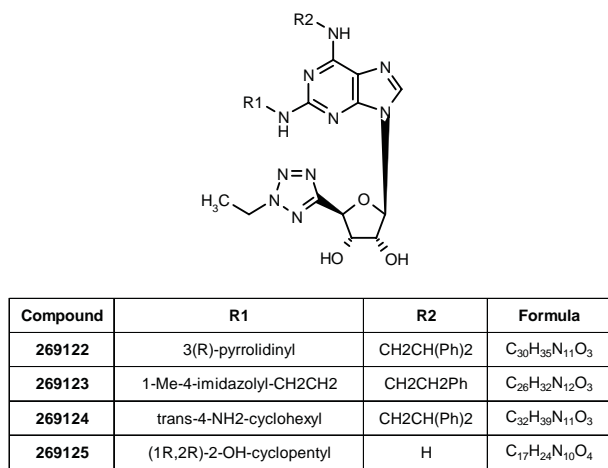
269121

(2*R*,3*R*,4*S*,5*R*)-2-[6-Amino-2-[1(*S*)-(hydroxymethyl)-2-phenylethylamino]purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diol



C₂₁ H₂₆ N₁₀ O₄; Mol wt: 482.5024

ACTION – Agent for the treatment of inflammatory disorders such as asthma and chronic obstructive pulmonary disease (COPD), a selective adenosine A_{2a} receptor agonist, as demonstrated in binding assays. Compound reduced antigen-induced lung eosinophil accumulation in sensitized guinea pigs with an ED₅₀ of 6 μg/l by inhalation. Other specifically claimed compounds from this series of 2-(purin-9-yl)-tetrahydrofuran-3,4-diol derivatives include the following:



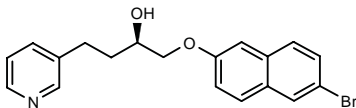
SOURCE – Glaxo Wellcome.

REFERENCES

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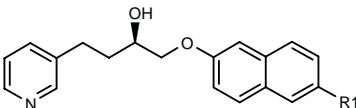
269202

1-(6-Bromo-2-naphthyloxy)-4-(3-pyridyl)-2(R)-butanol



C19 H18 Br N O2; Mol wt: 372.2602

ACTION – Agent for the treatment of allergic, inflammatory, autoimmune and proliferative disorders, particularly asthma and rhinitis, an inhibitor of the activation of hematopoietic cells including mast cells, neutrophils and eosinophils. Within this series of specifically claimed pyridine derivatives, the following are also included:



Compound	R1	Formula
269203	CH=CHCO2H	C ₂₂ H ₂₁ NO ₄
269204	CH2CH2CON(Me)2	C ₂₄ H ₂₈ N2O3
269205	CH2CH2CONHCH2CO2CH2Ph	C ₃₁ H ₃₂ N2O5
269206	4-morpholinyl-CH2CH2CO	C ₂₆ H ₃₀ N2O4
269207	CH2CH2CONHCH2CH2OH	C ₂₄ H ₂₈ N2O4
269208	1-Piz-CH2CH2CO	C ₂₆ H ₃₁ N3O3
269209	t-BuNHCO(CH2)6NHCOCH2CH2	C ₃₃ H ₄₆ N3O4

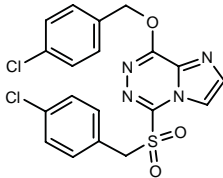
SOURCE – Astra.

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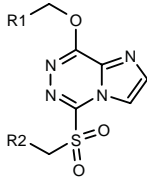
269335

8-(4-Chlorobenzoyloxy)-5-(4-chlorobenzylsulfonyl)-imidazo[1,2-d][1,2,4]triazine



C19 H14 Cl2 N4 O3 S; Mol wt: 449.3166

ACTION – Agent for the treatment of inflammatory, allergic, cardiovascular and bone and cartilage disorders, an inhibitor of the enzyme chymase (IC₅₀ = 0.0668 μM against activated human mast cell enzyme). Within this series of triazine sulfone derivatives, the following are also included:



Compound	R1	R2	Formula
269336	4-Me-Ph	4-Me-Ph	C ₂₁ H ₂₀ N4O3S
269337	Bu	Bu	C ₁₅ H ₂₄ N4O3S
269338	CO2Et	4-Cl-Ph	C ₁₆ H ₁₅ ClN4O5S

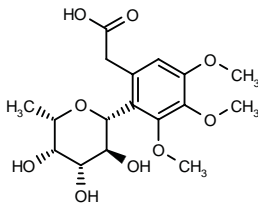
SOURCE – Teijin.

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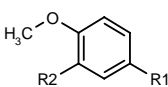
269400^{1,2}

2-[2-(6-Deoxy-β-L-galactopyranosyl)-3,4,5-trimethoxy-phenyl]acetic acid

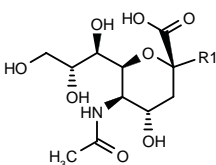


C17 H24 O9; Mol wt: 372.3676

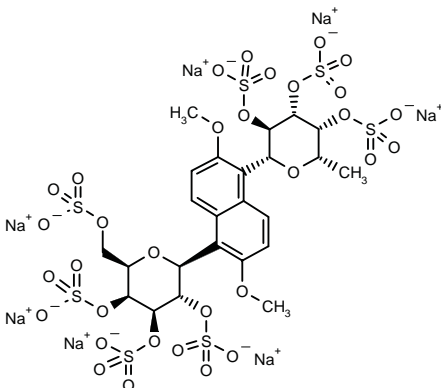
ACTION – Agent for the treatment or prevention of inflammatory disorders, autoimmune diseases, infections, cancer, reperfusion disorders, thrombosis, ulcers, wounds and osteoporosis that acts by inhibiting cell adhesion processes. *In vitro*, compound was found to inhibit the binding of P- and L-selectin, and it was reported to be active against antigen-induced eosinophil accumulation and asthma in guinea pigs. Within this series of aryl C-glycoside derivatives, the following are also specifically claimed:



Compound	R1	R2	Formula
269401 ^{1,2}	CH2CO2H	6-deoxy-β-L-galactopyranosyl	C ₁₅ H ₂₀ O ₇
269402 ^{1,2}	1-CO2H-cyclohexyl	6-deoxy-β-L-galactopyranosyl	C ₂₀ H ₂₈ O ₇
269403 ^{1,2}	(CH2)3CO2H	6-deoxy-β-L-galactopyranosyl	C ₁₇ H ₂₄ O ₇
269404 ^{1,2}	1-CO2H-cyclohexyl	β-D-galactopyranosyl	C ₂₀ H ₂₈ O ₈
269405 ^{1,2}	1-CO2H-cyclohexyl	6-deoxy-β-L-manopyranosyl	C ₂₀ H ₂₈ O ₇
269406 ^{1,2}	1-CO2H-cyclohexyl	β-D-xilopyranosyl	C ₁₉ H ₂₆ O ₇



Compound	R1	Formula
269407 ¹	2,4-(MeO)2-5-(6-deoxy-β-L-galactopyranosyl)-Ph	C ₂₈ H ₃₇ NO ₁₄
269408 ¹	2,6-(MeO)2-5-(6-deoxy-β-L-galactopyranosyl)-1-Naph	C ₂₉ H ₃₉ NO ₁₄



269409¹: C₂₄ H₂₅ Na₇ O₃₂ S₇

SOURCES – Glycomed; Sankyo.

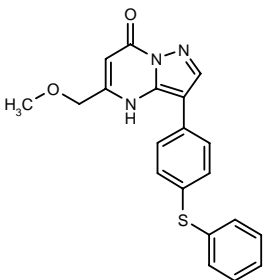
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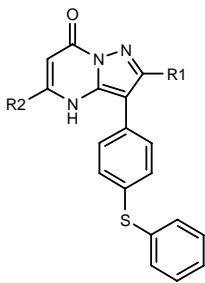
269410

5-(Methoxymethyl)-3-[4-(phenylsulfanyl)phenyl]-pyrazolo[1,5-a]pyrimidin-7(4H)-one



C₂₀ H₁₇ N₃ O₂ S; Mol wt: 363.4393

ACTION – Agent for the treatment of asthma and atopic dermatitis that acts by inhibiting the formation of nitric oxide (NO) *in vivo* and is also reported to inhibit the production of mediators such as cytokines, for example IL-4, IL-5 and IL-8, tumor necrosis factor-α (TNF-α), leukotrienes, PAF, prostaglandins, 5-lipoxygenase (5-LO) and granulocyte–macrophage colony-stimulating factor (GM-CSF). *In vitro*, it was found to inhibit NO formation in murine macrophage-derived RAW 264.7 cells stimulated with LPS at a concentration of 1 μM, while showing no cytotoxicity. In addition, it was found to inhibit TNF-α formation in RAW 264.7 cells at 10 and 100 μM, as well as IL-8 production in human epithelial A549 cells at 0.1-10 μM. It was also shown to inhibit 5-LO from rat basophilic leukemia-1 (RBL-1) cells, giving 68.0% inhibition at 1 μM. *In vivo*, compound was shown to be effective in an experimental model of late asthmatic response in guinea pigs at 10 mg/kg p.o., as well as in a model of contact hypersensitivity in mice at 2 mg/kg p.o. Within this series of pyrimidine derivatives, the following are also included:



Compound	R1	R2	Formula
269411	H	CH2OPh	C ₂₅ H ₁₉ N ₃ O ₂ S
269412	H	CH2OCH2CH2OMe	C ₂₂ H ₂₁ N ₃ O ₃ S
269413	H	t-BuOCH2CH2OCH2	C ₂₅ H ₂₇ N ₃ O ₃ S
269414	H	2-THF	C ₂₂ H ₁₉ N ₃ O ₂ S
269415	H	CH2CH2OMe	C ₂₁ H ₁₉ N ₃ O ₂ S
269416	H	CH(OMe)2	C ₂₁ H ₁₉ N ₃ O ₃ S
269417	H	CH2SMe	C ₂₀ H ₁₇ N ₃ O ₂ S
269418	CH2OMe	CH2OMe	C ₂₂ H ₂₁ N ₃ O ₃ S

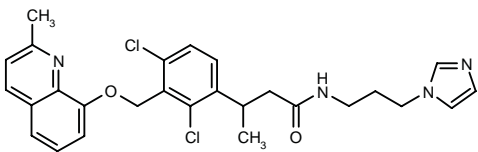
SOURCE – Otsuka.

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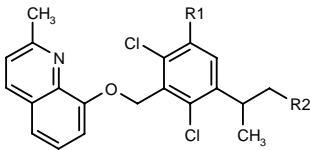
269442

3-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-phenyl]-N-[3-(1-imidazolyl)propyl]butyramide

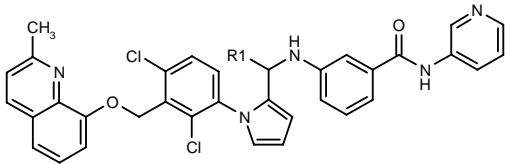


C₂₇ H₂₈ Cl₂ N₄ O₂; Mol wt: 511.4502

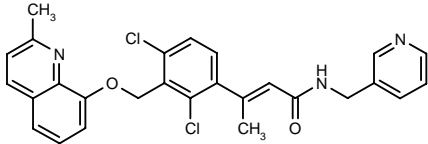
ACTION – Agent for the treatment of inflammatory, allergic and autoimmune diseases, pain, pancreatitis, etc., a bradykinin receptor antagonist, as demonstrated in a binding assay (98% inhibition of [³H]-bradykinin binding in guinea pig ileum preparations). Other representative compounds within this series of benzene derivatives include the following:



Compound	R1	R2	Formula
269443	H	4-NH2-PhCH2CH2NHCO	C ₂₉ H ₂₉ Cl ₂ N ₃ O ₂
269444	H	4-(3-PyrCH2NHCO)-PhCH2NHCO	C ₃₅ H ₃₂ Cl ₂ N ₄ O ₃
269445	NO2	1-imidazolyl-(CH2)3NHCO	C ₂₇ H ₂₇ Cl ₂ N ₅ O ₄
269447	H	4-(3-PyrCONH)-PhCH2NHCONH	C ₃₄ H ₃₁ Cl ₂ N ₅ O ₃



Compound	R1	Formula
269448	H	C ₃₄ H ₂₇ Cl ₂ N ₅ O ₂
269449	Ac	C ₃₆ H ₂₉ Cl ₂ N ₅ O ₃



269446: C27 H23 Cl2 N3 O2

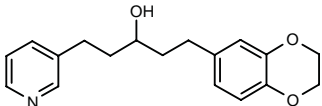
SOURCE – Kyowa Hakko.

REFERENCES

1. Hagihara, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Benzene derivs.* WO 9842672.

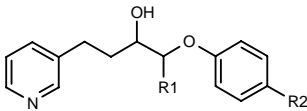
269521

1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-5-(3-pyridyl)-3-pentanol

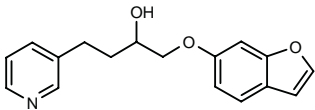


C18 H21 N O3; Mol wt: 299.3679

ACTION – Agent for the treatment or prevention of allergic, inflammatory, autoimmune, proliferative and hyperproliferative disorders, most particularly asthma and rhinitis, that acts by inhibiting the activation of cell types of hematopoietic lineage such as mast cells, neutrophils and eosinophils. Within this series of pyridine derivatives, the following are also specifically claimed:



Compound	R1	R2	Isomer	Formula
269522	H	5-Cl-2-thienyl	2R	C ₁₉ H ₁₈ ClNO ₂ S
269524	H	1,3-(Me)2-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl	2R	C ₂₁ H ₂₃ N ₃ O ₄
269525	H	2-oxo-1,2-dihydro-4-Pyr	2R	C ₂₀ H ₂₀ N ₂ O ₃
269526	H	1,3,4-oxadiazol-2-yl	2R	C ₁₇ H ₁₇ N ₃ O ₃
269527	Me	6-N(Me)2-2-Pyr	1S,2R	C ₂₃ H ₂₇ N ₃ O ₂
269528	Me	5-(NH2SO2)-2-thienyl	1S,2R	C ₂₀ H ₂₂ N ₂ O ₄ S ₂
269529	H	5-CN-3-Pyr	2R	C ₂₁ H ₁₉ N ₃ O ₂
269530	Me	1-[N(Me)2SO2]-4-pyrazolyl	1R,2S	C ₂₁ H ₂₆ N ₄ O ₄ S
269531	H	1-Me-5-CF3-6-oxo-1,6-dihydro-3-Pyr	2R	C ₂₂ H ₂₁ F ₃ N ₃ O ₃
269532	Me	5-(NH2SO2)-3-thienyl	1S,2R	C ₂₀ H ₂₂ N ₂ O ₄ S ₂



269523: C17 H17 N O3

SOURCE – Astra.

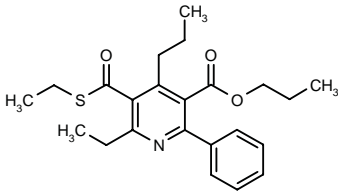
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MRS-1523

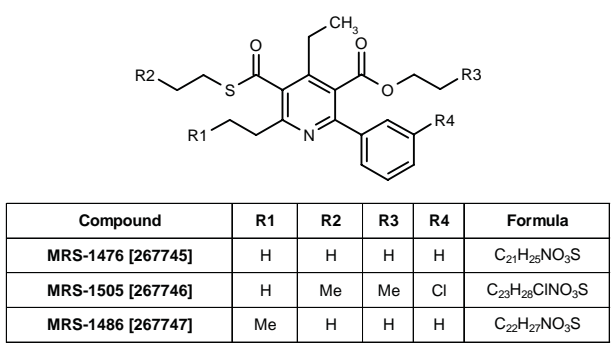
267744

6-Ethyl-5-(ethylsulfanylcarbonyl)-2-phenyl-4-propyl-pyridine-3-carboxylic acid propyl ester



C23 H29 N O3 S; Mol wt: 399.5521

ACTION – Adenosine A₃ receptor antagonist with high affinity for both rat and human A₃ receptors (K_i = 113 nM against [¹²⁵I]-AB-MECA binding to rat A₃ receptors expressed in CHO cells; K_i = 18.9 nM against [¹²⁵I]-AB-MECA binding to cloned human A₃ receptors expressed in HEK cells) and good selectivity relative to rat A₁ receptors (K_i = 15.6 μM). Potentially useful as an antiinflammatory, antiasthmatic or antiischemic agent. Other related compounds are:



SOURCE – National Institutes of Health, Bethesda, MD (US).

REFERENCES

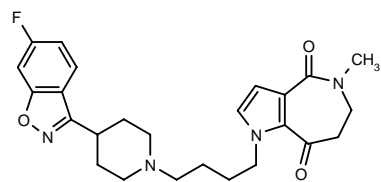
1. Li, A.-H. et al. *Structure-activity relationships and molecular modeling of 3,5-dialkyl-2,4-dialkylpyridine derivatives as selective A3 adenosine receptor antagonists.* J Med Chem 1998, 41(17): 3186.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

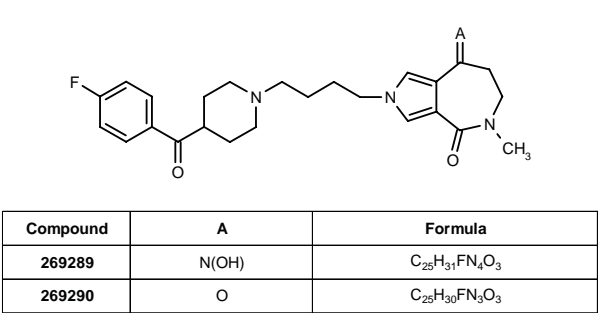
269287

1-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]butyl]-5-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-c]-azepine-4,8-dione



C₂₅ H₂₉ F N₄ O₃; Mol wt: 452.5271

ACTION – Antihypertensive and antiischemic agent with strong α_1 - and 5-HT₂ receptor-antagonist activity; α_1 -blocking effects were determined by measuring inhibition of norepinephrine-induced contractions of guinea pig thoracic aorta (27.8 and 14.0% of control [taken as 100%] at concentrations of 0.01 and 0.1 μM , respectively), and 5-HT₂-antagonist effects were evaluated by measuring inhibition of 5-HT-induced contractions of guinea pig superior mesenteric artery (80.8, 55.2 and 8.9% of control [taken as 100%] at concentrations of 0.01, 0.1 and 1 μM , respectively). Other representative compounds within this series of pyrroloazepine derivatives include the following:



269288: C₂₅ H₃₀ F N₃ O₃

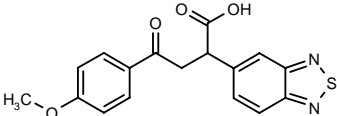
SOURCE – Suntory.

REFERENCES

1. Mizuno, A. et al. (Suntory Ltd.) *Pyrroloazepine cpds.* JP 98251258, WO 9841527.

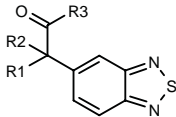
269315

2-(2,1,3-Benzothiadiazol-5-yl)-4-(4-methoxyphenyl)-4-oxobutyric acid



C₁₇ H₁₄ N₂ O₄ S; Mol wt: 342.3736

ACTION – Agent for the treatment of hypertension and heart failure, an endothelin receptor antagonist. Other specifically claimed compounds include the following:

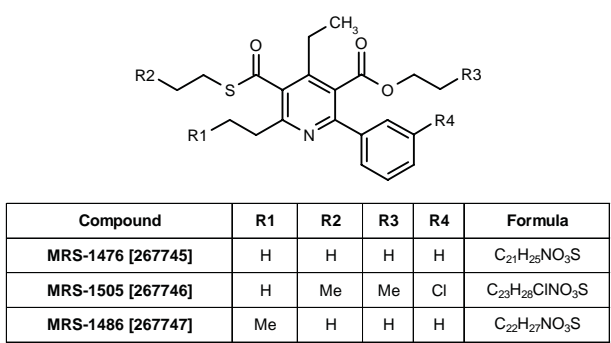


Compound	R1	R2	R3	Formula
269316	H	2,1,3-benzothia-diazol-5-yl-CH2	OH	C ₁₅ H ₁₀ N ₄ O ₂ S ₂
269317	H	4-(CO2Me)-PhCH2	OH	C ₁₇ H ₁₄ N ₂ O ₄ S
269318	H	4-(CO2Me)-PhCH2	4-i-Pr-Ph-SO2NH	C ₂₈ H ₂₈ N ₃ O ₅ S ₂
269319	H	4-CO2H-PhCH2	4-i-Pr-Ph-SO2NH	C ₂₈ H ₂₃ N ₃ O ₅ S ₂
269320	H	4-MeO-PhCH2	OH	C ₁₆ H ₁₄ N ₂ O ₃ S
269321	4-MeO-Ph-CH2	4-MeO-PhCOCH2	OH	C ₂₅ H ₂₂ N ₂ O ₅ S

SOURCE – Merck KGaA.

REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *Endothelin receptor antagonists.* WO 9841515.



SOURCE – National Institutes of Health, Bethesda, MD (US).

REFERENCES

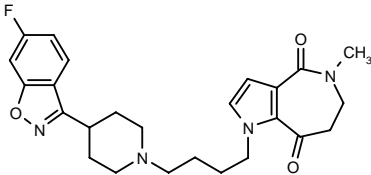
1. Li, A.-H. et al. *Structure-activity relationships and molecular modeling of 3,5-diacyl-2,4-dialkylpyridine derivatives as selective A3 adenosine receptor antagonists.* J Med Chem 1998, 41(17): 3186.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

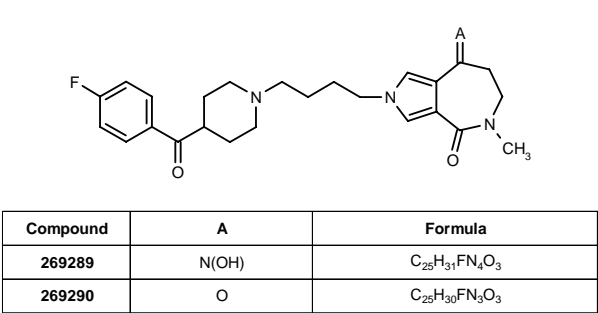
269287

1-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]butyl]-5-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-c]-azepine-4,8-dione



C₂₅ H₂₉ F N₄ O₃; Mol wt: 452.5271

ACTION – Antihypertensive and antiischemic agent with strong α₁- and 5-HT₂ receptor-antagonist activity; α₁-blocking effects were determined by measuring inhibition of norepinephrine-induced contractions of guinea pig thoracic aorta (27.8 and 14.0% of control [taken as 100%] at concentrations of 0.01 and 0.1 μM, respectively), and 5-HT₂-antagonist effects were evaluated by measuring inhibition of 5-HT-induced contractions of guinea pig superior mesenteric artery (80.8, 55.2 and 8.9% of control [taken as 100%] at concentrations of 0.01, 0.1 and 1 μM, respectively). Other representative compounds within this series of pyrroloazepine derivatives include the following:



269288: C₂₅ H₃₀ F N₃ O₃

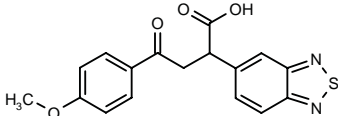
SOURCE – Suntory.

REFERENCES

1. Mizuno, A. et al. (Suntory Ltd.) *Pyrroloazepine cpds.* JP 98251258, WO 9841527.

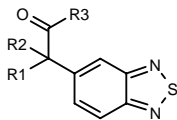
269315

2-(2,1,3-Benzothiadiazol-5-yl)-4-(4-methoxyphenyl)-4-oxobutyric acid



C₁₇ H₁₄ N₂ O₄ S; Mol wt: 342.3736

ACTION – Agent for the treatment of hypertension and heart failure, an endothelin receptor antagonist. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
269316	H	2,1,3-benzothia-diazol-5-yl-CH2	OH	C ₁₅ H ₁₀ N ₄ O ₂ S ₂
269317	H	4-(CO2Me)-PhCH2	OH	C ₁₇ H ₁₄ N ₂ O ₄ S
269318	H	4-(CO2Me)-PhCH2	4-i-Pr-Ph-SO2NH	C ₂₈ H ₂₈ N ₃ O ₅ S ₂
269319	H	4-CO2H-PhCH2	4-i-Pr-Ph-SO2NH	C ₂₈ H ₂₃ N ₃ O ₅ S ₂
269320	H	4-MeO-PhCH2	OH	C ₁₆ H ₁₄ N ₂ O ₃ S
269321	4-MeO-Ph-CH2	4-MeO-PhCOCH2	OH	C ₂₅ H ₂₂ N ₂ O ₅ S

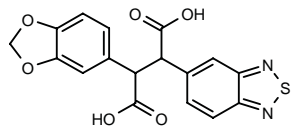
SOURCE – Merck KGaA.

REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *Endothelin receptor antagonists.* WO 9841515.

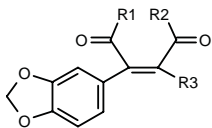
269322

2-(1,3-Benzodioxol-5-yl)-3-(2,1,3-benzothiadiazol-5-yl)succinic acid



C17 H12 N2 O6 S; Mol wt: 372.3558

ACTION – Endothelin receptor antagonist with high affinity for ET_A and ET_B subtypes, potentially useful for the treatment of hypertension, heart failure, renal failure, cerebral infarction, coronary disorders, renal, cerebral and myocardial ischemia, subarachnoid hemorrhage, inflammation, asthma and endotoxic shock. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
269323	OH	OH	1,3-benzodioxol-5-yl	C ₁₈ H ₁₂ O ₈
269324	N(Bu) ₂	OH	1,3-benzodioxol-5-yl	C ₂₆ H ₂₉ NO ₇
269325	-O-	-O-	1,3-benzodioxol-5-yl	C ₁₈ H ₁₀ O ₇
269326	-O-	-O-	Ph	C ₁₇ H ₁₀ O ₅

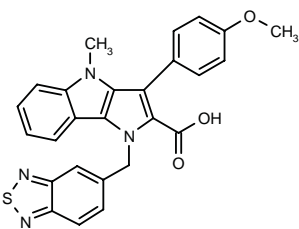
SOURCE – Merck KGaA.

REFERENCES

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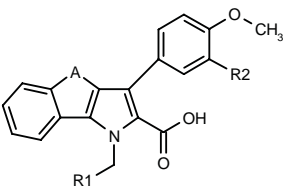
269698

1-(2,1,3-Benzothiadiazol-5-ylmethyl)-3-(4-methoxyphenyl)-4-methyl-1,4-dihydropyrrolo[3,2-*b*]indole-2-carboxylic acid



C26 H20 N4 O3 S; Mol wt: 468.5350

ACTION – Endothelin receptor antagonist with high affinity for ET_A and ET_B receptors, potentially useful for the treatment of hypertension, heart failure, renal failure, cerebral infarction, renal, cerebral and myocardial ischemia, subarachnoid hemorrhage, inflammation, asthma and endotoxic shock. Other specifically claimed tricyclic compounds include the following:



Compound	R1	R2	A	Formula
269699	2-MeO-Ph	H	N(Me)	C ₂₇ H ₂₄ N ₂ O ₄
269700	2,5-(MeO) ₂ -Ph	H	N(Me)	C ₂₈ H ₂₆ N ₂ O ₅
269701	1,3-benzodioxol-5-yl	H	N(Me)	C ₂₇ H ₂₂ N ₂ O ₅
269702	2,1,3-benzothiadiazol-5-yl	H	O	C ₂₅ H ₁₇ N ₃ O ₄ S
269703	2,1,3-benzothiadiazol-5-yl	H	S	C ₂₅ H ₁₇ N ₃ O ₃ S ₂
269704	2,1,3-benzothiadiazol-5-yl	OCH ₂ CO ₂ H	N(Me)	C ₂₈ H ₂₂ N ₄ O ₆ S
269705	2,1,3-benzothiadiazol-5-yl	OCH ₂ CO ₂ H	O	C ₂₇ H ₁₉ N ₃ O ₇ S
269706	2,1,3-benzothiadiazol-5-yl	OCH ₂ CO ₂ H	S	C ₂₇ H ₁₉ N ₃ O ₆ S ₂

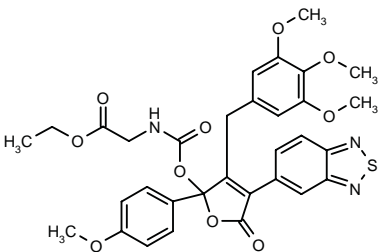
SOURCE – Merck KGaA.

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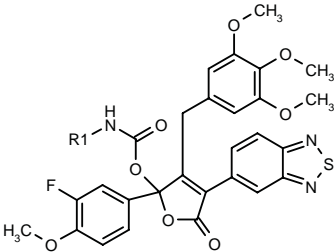
269810

N-[4-(2,1,3-Benzothiadiazol-5-yl)-2-(4-methoxyphenyl)-5-oxo-3-(3,4,5-trimethoxybenzyl)-2,5-dihydrofuran-2-yl]oxycarbonyl]glycine ethyl ester



C32 H31 N3 O10 S; Mol wt: 649.6739

ACTION – Agent for the treatment of hypertension, heart failure, renal failure, cerebral infarction, renal, cerebral and myocardial ischemia, subarachnoid hemorrhage, inflammation, asthma and endotoxic shock, an endothelin receptor antagonist with high affinity for ET_A and ET_B receptors. Within this series of specifically claimed 5*H*-furan-2-ones, the following are also included:



Compound	R1	Formula
269811	CH ₂ CO ₂ Et	C ₃₂ H ₃₀ FN ₃ O ₁₀ S
269812	1-Naph-CH ₂ CH ₂	C ₄₀ H ₃₄ FN ₃ O ₉ S
269813	CH(<i>i</i> -Pr)CO ₂ Et	C ₃₅ H ₃₆ FN ₃ O ₁₀ S

SOURCE – Merck KGaA.

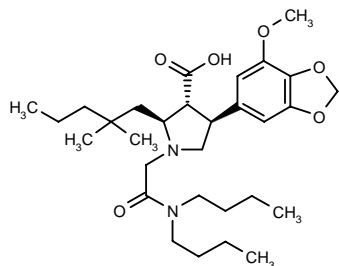
REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *Endothelin-receptor antagonists*. WO 9842702.

A-216546

267750

(2*S*,3*R*,4*S*)-1-[2-(Dibutylamino)-2-oxoethyl]-2-(2,2-dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)tetrahydro-1*H*-pyrrole-3-carboxylic acid



C30 H48 N2 O6; Mol wt: 532.7172

White solid.

ACTION – Potent, highly selective ET_A receptor antagonist, as shown in binding assays ($K_i = 0.46$ nM for human ET_A receptors; $K_i = 13,000$ nM for human ET_B receptors), with good oral bioavailability in rats (48%). Functional antagonist activity at this receptor was demonstrated by inhibition of ET-1-induced phosphoinositol hydrolysis in rat MMQ cells ($IC_{50} = 0.59$ nM). It was selected from a series of pyrrolidine-3-carboxylic acids as a potential backup compound to ABT-627 (A-147627).

SOURCE – Abbott.

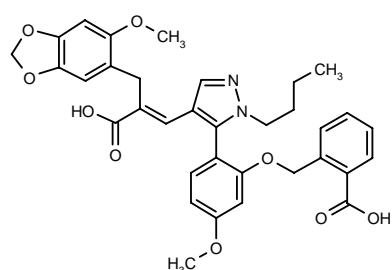
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3. Wu-Wong, J.R. et al. *Pharmacological characterization of A-216546: An orally active and highly selective antagonist for the type-A endothelin receptor*. FASEB J 1998, 12(4, Part 1): Abst 579.

SB-234551*

248947

2-[2-[1-Butyl-4-[2-carboxy-3-(6-methoxy-1,3-benzodioxol-5-yl)-1(*E*)-propenyl]pyrazol-5-yl]-5-methoxyphenoxy-methyl]benzoic acid



C34 H34 N2 O9; Mol wt: 614.6476

ACTION – High-affinity, selective, nonpeptide endothelin ET_A receptor antagonist ($K_i = 0.13$ and 500 nM, respectively, for displacing [¹²⁵I]-ET-1 binding to cloned human ET_A and ET_B receptors). In functional studies, compound antagonized ET_A receptor-mediated contractions in isolated rat aorta ($K_b = 1.9$ nM) and isolated human pulmonary artery ($K_b = 1.0$ nM), with much weaker activity against ET_B receptor-mediated sarafotoxin S6c-induced contractions in isolated rabbit pulmonary artery ($K_b = 555$ nM). *In vivo*, it inhibited the pressor response to exogenous ET-1 in conscious normotensive rats dose-dependently at 0.1-1.0 mg/kg i.v. It showed an oral bioavailability of 30% in rats.

SOURCE – SmithKline Beecham.

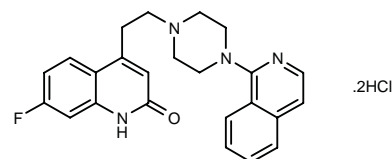
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2. Brooks, D.P. et al. *SB 234551, a novel endothelin-A receptor antagonist, unmasks endothelin-induced renal vasodilatation in the dog*. J Cardiovasc Pharmacol 1998, 31(Suppl. 1): S339.
3. Brooks, D.P. et al. *The novel ET_A receptor antagonist, SB 234551, unmasks endothelin-mediated vasodilation and attenuates radio-contrast-induced nephropathy in dogs*. J Am Soc Nephrol 1997, Abst A2795.
4. Ohlstein, E.H. et al. *Nonpeptide endothelin receptor antagonists. XI. Pharmacological characterization of SB 234551, a high-affinity and selective nonpeptide ETA receptor antagonist*. J Pharmacol Exp Ther 1998, 286(2): 650.
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*Identified compound **248947** Drug Data Report 1997, 019(06): 0514.

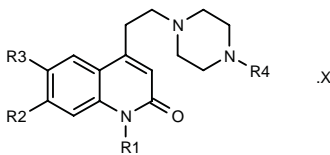
269823

7-Fluoro-4-[2-[4-(1-isoquinolinyl)piperazin-1-yl]ethyl]-quinolin-2(1*H*)-one dihydrochloride



C24 H23 F N4 O . 2HCl; Mol wt: 475.3925

ACTION – 5-HT₂ and 5-HT₁-like receptor antagonist claimed for the treatment or prevention of various types of hypertension and ischemic disorders, heart failure, thrombosis, restenosis following angioplasty, atherosclerosis, pulmonary dysfunction and microcirculatory disorders, as well as coronary or peripheral vasospasm. A representative compound from a series of quinolin-2(1*H*)-one derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	X	Formula
269824	H	F	H	5-OH-1-isoquinolinyl	2HCl	C ₂₄ H ₂₃ FN ₄ O ₂ .2HCl
269825	H	F	H	7-(MeSO ₂ NH)-1-isoquinolinyl		C ₂₅ H ₂₆ FN ₅ O ₃ S
269826	Me	H	Cl	furo[3,2-c]pyridin-4-yl	2HCl	C ₂₃ H ₂₃ ClN ₄ O ₂ .2HCl
269827	H	F	H	1-Me-1H-pyrrolo-[3,2-c]pyridin-4-yl	2HCl	C ₂₃ H ₂₄ FN ₅ O.2HCl
269828	H	F	H	1,3-thiazolo[4,5-c]-pyridin-4-yl	2HCl	C ₂₁ H ₂₀ FN ₅ OS.2HCl
269829	Me	F	H	1H-1,2,3-triazolo-[4,5-c]pyridin-4-yl	2HCl	C ₂₁ H ₂₂ FN ₇ O.2HCl
269830	H	F	H	2,7-naphthyridin-1-yl		C ₂₃ H ₂₂ FN ₅ O
269831	H	F	H	7-(EtOCO)-1-isoquinolinyl	2HCl	C ₂₇ H ₂₇ FN ₄ O ₄ .2HCl
269832	H	F	H	7-[N(Me)2SO ₂ O]-1-isoquinolinyl		C ₂₆ H ₂₈ FN ₅ O ₄ S

SOURCE – Synthélabo.

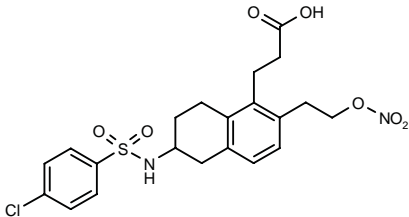
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES

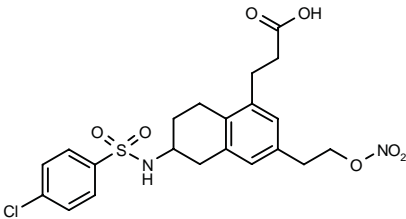
268583

3-[6-(4-Chlorophenylsulfonamido)-2-(2-nitrooxyethyl)-5,6,7,8-tetrahydro-1-naphthyl]propionic acid



C21 H23 Cl N2 O7 S; Mol wt: 482.9387

ACTION – TxA₂ receptor antagonist with additional nitric oxide (NO)-donating properties, potentially useful in the treatment of cardiovascular and cerebrovascular disorders, thrombotic disorders, restenosis, vascular complications associated with diabetes, hypertension, atherosclerosis, Raynaud’s disease, renal diseases, asthma and migraine. Compound inhibited U-46619-induced aggregation of human platelet-rich plasma (PRP) with an IC₅₀ value of 140 nM and it inhibited U-46619-induced rabbit saphenous vein contractions with a pA₂ value of 9.5. Another compound from this series of benzenesulfonamide derivatives is:



268584: C21 H23 Cl N2 O7 S

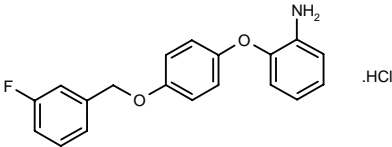
SOURCE – ADIR.

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1. Lavielle, G. et al. (ADIR et Cie.) Benzenesulfonamide derivs., process for their preparation and pharmaceutical compsns. containing them. EP 864561, JP 98251217.

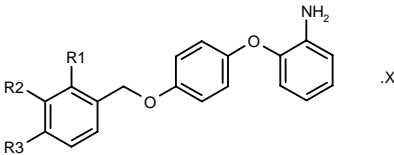
268795

2-[4-(3-Fluorobenzoyloxy)phenoxy]aniline hydrochloride



C19 H16 F N O2 . HCl; Mol wt: 345.7993

ACTION – Antiischemic agent that acts by virtue of its Na⁺/Ca⁺ exchange-inhibitory activity, as demonstrated *in vitro* in membranes of canine ventricular muscle (IC₅₀ = 0.87 μM) and also by inhibition of the increase in Ca²⁺ levels in rat ventricular myocardial cells (IC₅₀ = 0.63 μM). Other exemplified 2-phenoxyaniline derivatives include the following:



Compound	R1	R2	R3	X	Formula
268796	H	NH2	H	2HCl	C ₁₉ H ₁₈ N ₂ O ₂ .HCl
268797	H	H	F		C ₁₉ H ₁₆ FNO ₂
268798	Me	H	H	HCl	C ₂₀ H ₁₉ NO ₂ .HCl
268799	H	Cl	H	HCl	C ₁₉ H ₁₆ ClNO ₂ .HCl
268800	H	CO ₂ Me	H	HCl	C ₂₁ H ₁₉ NO ₄ .HCl
268801	H	Br	H	HCl	C ₁₉ H ₁₆ BrNO ₂ .HCl
268802	H	CF ₃	H	HCl	C ₂₀ H ₁₆ F ₃ NO ₂ .HCl

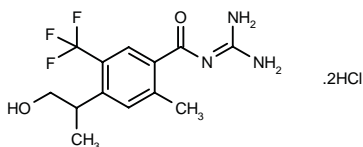
SOURCE – Taisho.

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269027

N-[4-(2-Hydroxy-1-methylethyl)-2-methyl-5-(trifluoromethyl)benzoyl]guanidine dihydrochloride



C13 H16 F3 N3 O2 . 2HCl; Mol wt: 376.2042

ACTION – Inhibitor of Na⁺/H⁺ exchange (IC₅₀ = 0.0012 μM in rabbit erythrocytes) reported to possess improved water solubility relative to structurally similar compounds and to be free of salidiuretic effects. Potentially useful for the treatment of myocardial infarction, angina pectoris and cardiac and cerebral ischemic disorders. Compound is also reported to inhibit the proliferation of cells such as fibroblasts and smooth muscle cells and is therefore expected to be useful in the treatment of atherosclerosis, cancer, fibrotic disorders and prostatic hypertrophy or hyperplasia.

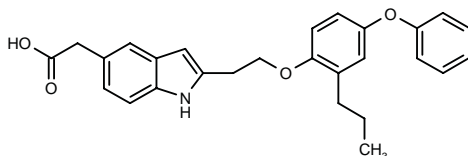
SOURCE – Hoechst Marion Roussel.

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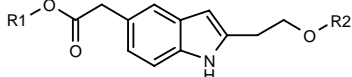
269117

2-[2-[2-(4-Phenoxy-2-propylphenoxy)ethyl]-1*H*-indol-5-yl]-acetic acid

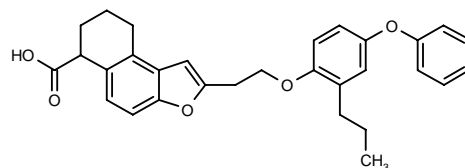


C27 H27 N O4; Mol wt: 429.5133

ACTION – Agent for the treatment of diabetes and related diseases, diabetic nephropathy, pancreatitis, obesity, hyperglycemia, hyperlipidemia, restenosis and, particularly, atherosclerosis that lowers or modulates triglyceride levels and/or cholesterol levels and increases plasma HDL cholesterol levels. It acts by interacting with the peroxisome proliferator-activated receptor (PPAR) family of receptors, particularly the PPARδ subtype. Other related compounds include the following:



Compound	R1	R2	Formula
269118	Me	4-(PhO)-2-Pr-Ph	C ₂₈ H ₂₉ NO ₄
269119	H	3-(PhCH ₂ CH ₂)-7-Pr-6-benzisoxazolyl	C ₃₀ H ₃₀ N ₂ O ₄



269120: C30 H30 O5

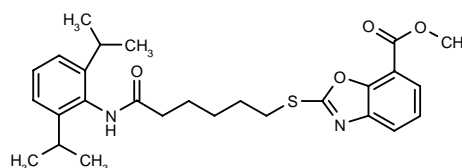
SOURCE – Merck & Co.

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1. Adams, A.D. et al. (Merck & Co., Inc.) *Antidiabetic agents*. WO 9827974.

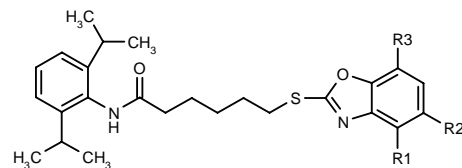
269433

2-[5-[*N*-(2,6-Diisopropylphenyl)carbamoyl]pentyl-sulfanyl]benzoxazole-7-carboxylic acid methyl ester

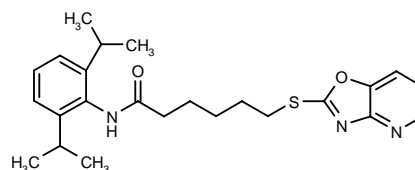


C27 H34 N2 O4 S; Mol wt: 482.6416

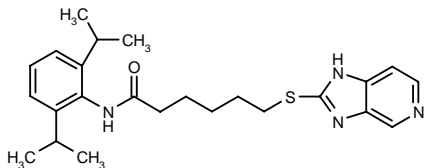
ACTION – Antiatherosclerotic agent, an ACAT inhibitor with selectivity for the enzyme present in blood vessel wall (IC₅₀ = 0.032 μM using rabbit enzyme) relative to enzyme from small intestine (IC₅₀ = 0.33 μM using rabbit enzyme). Antifoaming activity was determined by measuring ACAT inhibition in J774 cells (IC₅₀ = 0.098 μM) and HepG2 cells (IC₅₀ = 29.76 μM; ratio HepG2/J774 = 303.4). A representative compound from a series of anilide derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
269436	CH ₂ N(Me) ₂	H	H	C ₂₈ H ₃₆ N ₃ O ₂ S
269437	N(Me) ₂	H	H	C ₂₇ H ₃₇ N ₃ O ₂ S
269438	H	OCH ₂ Ph	H	C ₃₂ H ₃₈ N ₂ O ₃ S
269439	H	CO ₂ Me	H	C ₂₇ H ₃₄ N ₂ O ₄ S
269440	H	N(Me) ₂	H	C ₂₇ H ₃₇ N ₃ O ₂ S
269441	H	H	N(Me) ₂	C ₂₇ H ₃₇ N ₃ O ₂ S



269434: C24 H31 N3 O2 S



269435: C24 H32 N4 O S

SOURCE – Kowa.

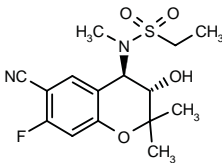
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ANTIARRHYTHMIC DRUGS

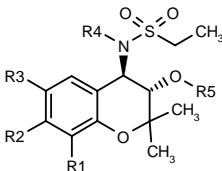
268747

trans-N-(6-Cyano-7-fluoro-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)-*N*-methylethanesulfonamide

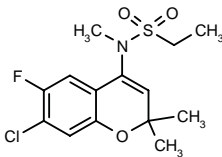


C15 H19 F N2 O4 S; Mol wt: 342.3891

ACTION – Antiarrhythmic agent, an inhibitor of the slow delayed rectifier K⁺ (K_{V(s)}) channel. Other exemplified sulfonamide-substituted chromane derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
268748	H	Cl	CN	Me	H	C ₁₅ H ₁₉ ClN ₂ O ₄ S
268749	H	Cl	CN	Me	Ac	C ₁₇ H ₂₁ ClN ₂ O ₅ S
268750	H	Cl	F	Me	H	C ₁₄ H ₁₉ ClFNO ₄ S
268751	H	Cl	F	Bu	H	C ₁₇ H ₂₅ ClFNO ₄ S
268752	H	Cl	F	Me	Ac	C ₁₆ H ₂₁ ClFNO ₅ S
268754	Cl	H	Cl	Me	H	C ₁₄ H ₁₉ Cl ₂ NO ₄ S
268755	Cl	H	Cl	Me	Ac	C ₁₆ H ₂₁ Cl ₂ NO ₅ S
268756	Cl	H	Cl	Bu	H	C ₁₇ H ₂₅ Cl ₂ NO ₄ S



268753: C14 H17 Cl F N O3 S

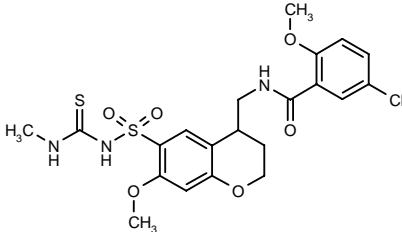
SOURCE – Hoechst Marion Roussel.

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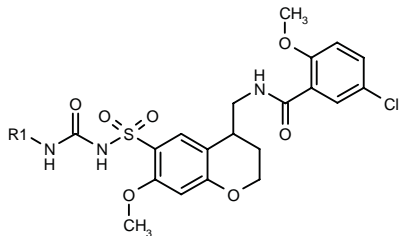
268888

5-Chloro-2-methoxy-*N*-[7-methoxy-6-(*N*'-methylthioureidosulfonyl)-3,4-dihydro-2*H*-1-benzopyran-4-ylmethyl]benzamide



C21 H24 Cl N3 O6 S2; Mol wt: 514.0206

ACTION – Antiarrhythmic agent with the ability to prolong the action potential duration (APD₉₅) in guinea pig cardiomyocytes exposed to the potassium channel opener rimakalim (from < 40 to 169 ± 16 ms vs. 164 ± 23 ms in controls). Potentially useful for preventing sudden cardiac death and for the treatment of cardiac insufficiency and heart failure resulting from shock. Other representative compounds within this series of specifically claimed substituted chromanysulfonyl(thio)ureas include the following:



Compound	R1	Formula
268889	Me	C ₂₁ H ₂₄ ClN ₃ O ₇ S
268890	Et	C ₂₂ H ₂₆ ClN ₃ O ₇ S
268891	Pr	C ₂₃ H ₂₈ ClN ₃ O ₇ S

SOURCE – Hoechst Marion Roussel.

REFERENCES

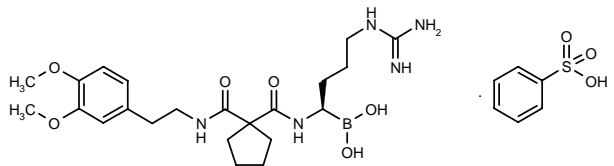
1. Englert, H.C. et al. (Hoechst AG) *Subst. chromanysulfonyl(thio)ureas, processing for their preparation and pharmaceutical uses thereof*. US 5811448.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

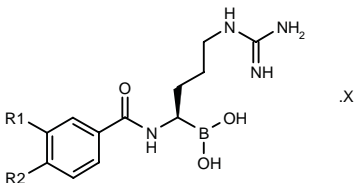
268762

1-(R)-[1-[N-2-(3,4-Dimethoxyphenyl)ethyl]carbamoyl]-cyclopentylcarboxamido]-4-guanidinobutylboronic acid benzenesulfonate

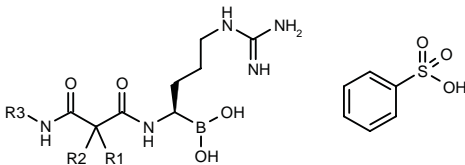


C22 H36 B N5 O6 . C6 H6 O3 S; Mol wt: 635.5428

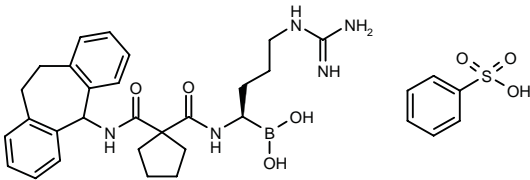
ACTION – Anticoagulant that acts as an inhibitor of trypsin-like serine proteases, particularly human thrombin (IC₅₀ = 4.0 nM). It produced marked prolongation of the thrombin time (TT) in human plasma, doubling it at 0.29 μM. Compound was not associated with thrombopenia after oral administration to dogs at a dose of 5 mg/kg, whereas it increased the TT > 30% after 1 h and 24% after 4 h. Other exemplified boronic acid derivatives include the following:



Compound	R1	R2	Formula
268763	H	4-MeO-bicyclo-[2.2.2]oct-1-yl	C ₂₁ H ₃₃ BN ₅ O ₄ .HCl
268765	H	4-OH-bicyclo-[2.2.2]oct-1-yl	C ₂₀ H ₃₁ BN ₄ O ₄ .HCl
268767	4-MeO-bicyclo-[2.2.2]oct-1-yl	H	C ₂₁ H ₃₃ BN ₄ O ₄ .HCl



Compound	R1	R2	R3	Formula
268764	Me	Me	CH2Ph	C ₁₇ H ₂₈ BN ₅ O ₄ .C ₆ H ₆ O ₃ S
268766	-(CH2)4-		CH2Ph	C ₁₉ H ₃₀ BN ₅ O ₄ .C ₆ H ₆ O ₃ S
268769	-(CH2)4-		CH2CH2Ph	C ₂₀ H ₃₂ BN ₅ O ₄ .C ₆ H ₆ O ₃ S
268770	-(CH2)4-		CH(Ph)2	C ₂₅ H ₃₄ BN ₅ O ₄ .C ₆ H ₆ O ₃ S



268768: C27 H36 B N5 O4 . C6 H6 O3 S

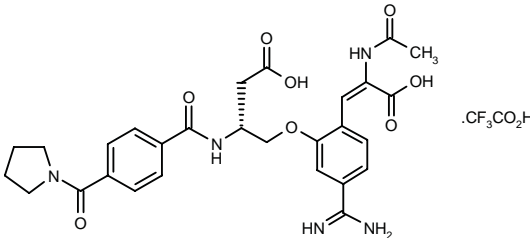
SOURCE – ADIR.

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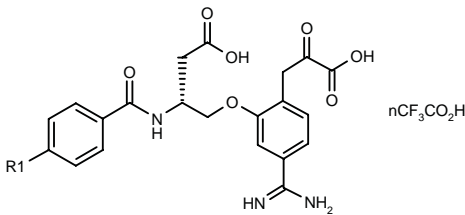
269150

2-Acetamido-3-[4-amidino-2-[3-carboxy-2(R)-[4-(pyrrolidin-1-ylcarbonyl)benzamido]propoxy]phenyl]-2(E)-propenoic acid trifluoroacetate



C28 H31 N5 O8 . C2 H F3 O2; Mol wt: 679.6018

ACTION – Anticoagulant, an inhibitor of human factor Xa (pIC₅₀ = 8.4) with selectivity relative to human thrombin (pIC₅₀ = 3.7). Within a wide series of benzamide derivatives, the following are also included:



Compound	R1	n	Formula
269151	1-[C(=NH)Me]-4-Pip-O	2	C ₂₈ H ₃₃ N ₅ O ₈ .2C ₂ HF ₃ O ₂
269152	1-pyrrolidinyl-SO2	1	C ₂₅ H ₂₈ N ₄ O ₉ S.C ₂ HF ₃ O ₂
269153	C(=NH)NH2	2	C ₂₂ H ₂₃ N ₅ O ₇ .2C ₂ HF ₃ O ₂
269154	CON(Me)2	1	C ₂₄ H ₂₆ N ₄ O ₈ .C ₂ HF ₃ O ₂

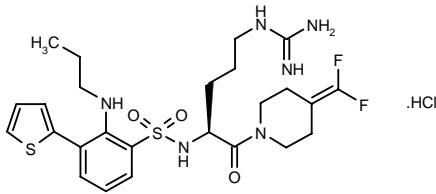
SOURCE – Ajinomoto.

REFERENCES

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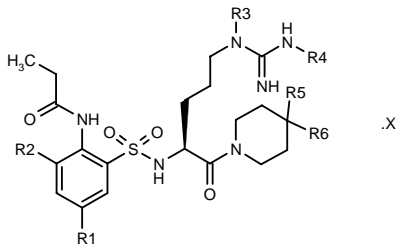
269801

4-(Difluoromethylene)-1-[N^α-[2-(propylamino)-3-(2-thienyl)phenylsulfonyl]-L-arginyl]piperidine hydrochloride



C25 H34 F2 N6 O3 S2 . HCl; Mol wt: 605.1715

ACTION – Anticoagulant and antithrombotic agent with thrombin-inhibitory activity. A representative compound from a series of N-(arginy)benzenesulfonamide derivatives, wherein the following are also included:



Compound	R1	R2	R3=R4	R5	R6	X	Formula
269802	F	2-Pyr	H	Et	H	HCl	C ₂₇ H ₃₈ FN ₇ O ₄ S .HCl
269803	H	cyclopentyl	H	-CF(Me)-		HCl	C ₂₇ H ₄₁ FN ₆ O ₄ S .HCl
269804	H	Ph	CO ₂ Et	Et	H	HCl	C ₃₄ H ₄₈ N ₆ O ₈ S .HCl
269805	H	2-thienyl	H	CH ₂ OH	H	HCl	C ₂₅ H ₃₆ N ₆ O ₅ S ₂ .HCl
269806	H	2-thienyl	H	CF ₃	OH	HCl	C ₂₅ H ₃₃ F ₃ N ₆ O ₅ S ₂ .HCl
269807	H	3-Me-Ph	H	-CF ₂ -		HCl	C ₂₈ H ₃₆ F ₂ N ₆ O ₄ S .HCl
269808	F	2-thienyl	Me	Et	H	HCl	C ₂₇ H ₃₉ FN ₆ O ₄ S ₂ .HCl
269809	H	2-thienyl	allyl-OCO	-CF ₂ -			C ₃₃ H ₄₀ F ₂ N ₆ O ₆ S ₂

SOURCE – Synthélabo.

REFERENCES

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BEMIPARIN SODIUM

Prop INN

224686

Sodium salt of depolymerized heparin obtained by alkaline degradation of quaternary ammonium salt of heparin from pork intestinal mucosa; the majority of the components have a 2-O-sulfo-4-enepyranosuronic acid structure at the nonreducing end and a 2-N,6-O-disulfo-D-glucosamine structure at the reducing end of their chain; the average relative molecular mass is about 3600 (3000-4200); the degree of sulfatation is about 2 per disaccharidic unit

RO-11⁺

ACTION – Low-molecular-weight heparin.

INDICATION – Prevention of thromboembolic disease in patients undergoing moderate-risk general surgery or high-risk orthopedic surgery.

PRESENTATION – Preloaded syringes for s.c. administration, 2500 IU (anti-factor Xa)/0.2 ml and 3500 IU (anti-factor Xa)/0.2 ml.

PROPRIETARY NAME – Hibor (ES).

SOURCE – Rovi.

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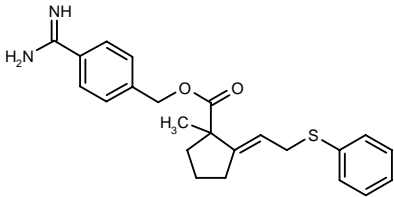
12. *Rovi introduces LMW heparin in Spain*. Prous Science Daily Essentials 1998, Oct 7.

*Drug Data Report 1995, 017(10): 0915.

ORG-34092

267804

1-Methyl-2(E)-[2-(phenylsulfanyl)ethylidene]cyclopentanecarboxylic acid 4-(amidino)benzyl ester



C23 H26 N2 O2 S; Mol wt: 394.5364

ACTION – Nonpeptide direct thrombin inhibitor from a series of molecules mimicking the D-Phe-Pro-Arg shape.

SOURCE – Organon.

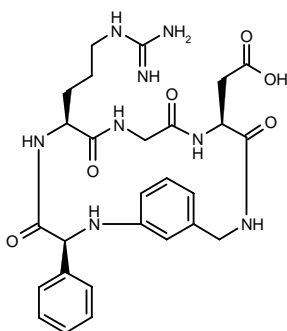
REFERENCES

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ANTIPLATELET THERAPY

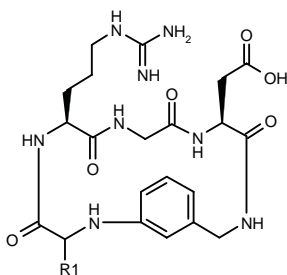
269126

(3*S*,6*S*,12*S*)-2-[6-(3-Guanidinopropyl)-3-phenyl]-4,7,10,13-tetraoxo-2,5,8,11,14-pentaazabicyclo[14.3.1]eicosa-1(20),16,18-trien-12-yl]acetic acid



C27 H34 N8 O6; Mol wt: 566.6156

ACTION – Integrin receptor antagonist that inhibits fibrinogen (gplIb/IIIa) receptor binding, with potential in the treatment or prevention of circulatory disorders, thrombosis, myocardial infarction, coronary heart disease, arteriosclerosis, cancer, osteoporosis, inflammation and microbial infections. Other specifically claimed compounds from this series of cyclic peptide derivatives include the following:



Compound	R1	Isomer	Formula
269127	Ph	R	C ₂₇ H ₃₄ N ₈ O ₆
269128	i-Pr	S	C ₂₄ H ₃₆ N ₈ O ₆
269129	i-Pr	R	C ₂₄ H ₃₆ N ₈ O ₆
269130	CH ₂ Ph	S	C ₂₈ H ₃₆ N ₈ O ₆
269131	CH ₂ Ph	R	C ₂₈ H ₃₆ N ₈ O ₆
269132	H		C ₂₁ H ₃₀ N ₈ O ₆

SOURCE – Merck KGaA.

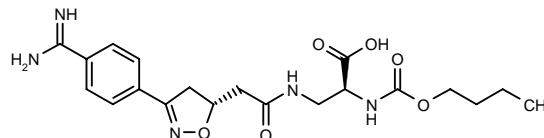
REFERENCES

1. Hölzemann, G. et al. (Merck Patent GmbH) *Cyclic peptide derivs*. WO 9827112.

XV-459

244583

3-[3-(4-Amidinophenyl)-4,5-dihydroisoxazol-5(*R*)-ylacetamido]-2(*S*)-(butoxycarbonylamino)propionic acid



C20 H27 N5 O6; Mol wt: 433.4623

ACTION – The active form of roxifiban acetate*, a high-affinity small-molecule gplIb/IIIa receptor antagonist shown to potently inhibit (IC₅₀ = 0.030-0.60 μM) ADP-, thrombin receptor agonist peptide (TRAP)- or collagen-induced human platelet aggregation; ADP-induced aggregation was also inhibited in both dog and baboon platelets (IC₅₀ = 0.027 and 0.040 μM, respectively). Maximum antiaggregatory responses were observed at 50-> 80% receptor occupancy and high-affinity binding was demonstrated to both activated and unactivated human platelets. The relatively slow dissociation rate from human platelet gplIb/IIIa receptors suggests the feasibility of once-daily oral dosing.

SOURCE – DuPont Pharmaceuticals.

REFERENCES

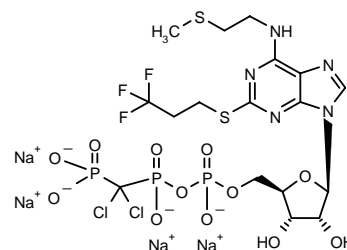
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2. Kapil, R.P. et al. *Nonlinear pharmacokinetics of a novel platelet glycoprotein IIb/IIIa receptor antagonist, XV459, in beagle dogs*. Pharm Res 1996, 13(9, Suppl.): Abst PPDM 8417.
3. Mousa, S.A. et al. *Antiplatelet efficacy of XV459, a novel nonpeptide platelet GPIIb/IIIa antagonist: Comparative platelet binding profiles with c7E3*. J Pharmacol Exp Ther 1998, 286(3): 1277.
4. Xue, C.-B. et al. *Discovery of an orally active series of isoxazoline glycoprotein IIb/IIIa antagonists*. J Med Chem 1997, 40(13): 2064.

*See **DMP-754** Drug Data Rep 1996, 018(09): 0803.

AR-C69931MX

259645

5'-O-[[[Dichloro(phosphono)methyl](hydroxy)phosphoryl-oxy](hydroxy)phosphoryl]-N-[2-(methylsulfanyl)ethyl]-2-(3,3,3-trifluoropropylsulfanyl)adenosine tetrasodium salt



C17 H21 Cl2 F3 N5 Na4 O12 P3 S2; Mol wt: 864.2899

ACTION – Antithrombotic agent, a potent and selective antagonist of the platelet P2T purinoceptor and competitive inhibitor of ADP-induced platelet aggregation (pIC₅₀ = 9.35). It exhibits a short duration of action as a consequence of rapid metabolic elimination. Presently undergoing phase II clinical trials as an i.v. antithrombotic agent, with potential in acute coronary syndromes patients.

SOURCE – Astra Charnwood.

REFERENCES

1. Bland, C. and Steele, G. (Astra Pharmaceuticals Ltd.;Astra AB) *Pharmaceutical compsns. for freeze drying*. WO 9828009.

2. Ingall, A.H. et al. (Fisons plc) *N-Alkyl-2-substd. ATP analogues*. EP 683789, JP 96506335, US 5721219, WO 9418216.

3. Gardner, J. et al. *The bioanalysis of a novel cardiovascular drug with high clearance*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.263.

4. Ingall, A.H. et al. *Short-acting antagonists of the platelet P2T-receptor - Beyond phosphates*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.280.

5. Kindon, N.D. et al. *SAR studies on AR-C 69931MX, a potent and selective intravenous anti-aggregatory/anti-thrombotic agent with a novel mechanism of action*. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.281.

6. Storey, R.F. et al. *In vitro effects of the novel platelet adenosine diphosphate receptor (P2T) antagonist AR-C69931MX and aspirin on platelet aggregation in human whole blood: A potential new therapy for arterial thrombosis*. Circulation 1998, 98(17, Suppl.): Abst 2949.

7. Storey, R.F. et al. *Potential therapeutic effects of the novel platelet adenosine diphosphate receptor P2T antagonist, AR-C69931MX, as assessed by in vitro studies in human whole blood. A possible adjunct to aspirin therapy?* Eur Heart J 1998, 19(Suppl.): Abst P493.

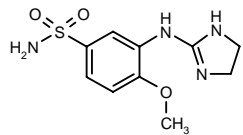
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RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

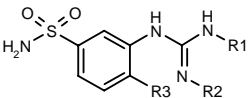
269268

3-(4,5-Dihydro-1H-imidazol-2-ylamino)-4-methoxy-benzenesulfonamide



C10 H14 N4 O3 S; Mol wt: 270.3116

ACTION – Agent for the treatment of stress urinary incontinence that acts on α-adrenoceptors; it was found to have marked urethral contractile activity but weak arterial effects. Other specifically claimed benzenesulfonamide derivatives include the following:



Compound	R1	R2	R3	Formula
269269	-(CH2)2-		Me	C ₁₀ H ₁₄ N ₄ O ₂ S
269270	-(CH2)2-		H	C ₉ H ₁₂ N ₄ O ₂ S
269271	-(CH2)3-		OMe	C ₁₁ H ₁₆ N ₄ O ₃ S
269272	H	Me	OMe	C ₉ H ₁₄ N ₄ O ₃ S

SOURCE – Synthélabo.

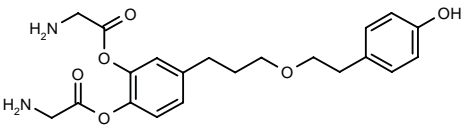
REFERENCES

1. Philippo, C. et al. (Synthélabo) *Benzenesulphonamide derivs., preparation and application thereof in therapy*. WO 9842679.

TREATMENT OF RENAL DISEASES

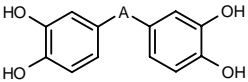
269586

4-[2-[3-[3,4-Bis(glycyloxy)phenyl]propoxy]ethyl]phenol

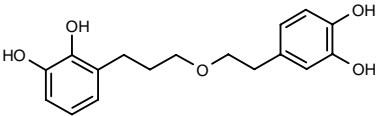


C21 H26 N2 O6; Mol wt: 402.4444

ACTION – Agent for the treatment of renal diseases proven to potently reduce proteinuria and serum cholesterol, BUN and creatinine levels in a murine model of nephritis following oral administration. A representative compound from a series of catechol derivatives, wherein the following are also included:



Compound	A	Formula
269587	-(CH2CH2OCH2CH2)-	C ₁₆ H ₁₈ O ₅
269589	-(CH2)3OCH2CH2-	C ₁₇ H ₂₀ O ₅
269590	-(CH2CH2SCH2CH2)-	C ₁₆ H ₁₈ O ₄ S
269591	-(CH2SCH2)-	C ₁₄ H ₁₄ O ₄ S



269588: C17 H20 O5

SOURCE – Tsumura.

REFERENCES

1. Hasegawa, Y. et al. (Tsumura & Co.) *Substd. catechol derivs*. JP 98273464.

ACTION – Antithrombotic agent, a potent and selective antagonist of the platelet P2T purinoceptor and competitive inhibitor of ADP-induced platelet aggregation (pIC₅₀ = 9.35). It exhibits a short duration of action as a consequence of rapid metabolic elimination. Presently undergoing phase II clinical trials as an i.v. antithrombotic agent, with potential in acute coronary syndromes patients.

SOURCE – Astra Charnwood.

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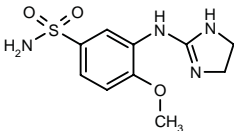
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RENAL–UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

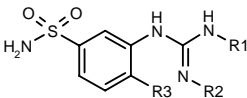
269268

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269272	H	Me	OMe	C ₉ H ₁₄ N ₄ O ₃ S

SOURCE – Synthélabo.

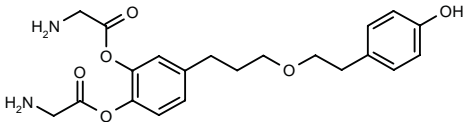
REFERENCES

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TREATMENT OF RENAL DISEASES

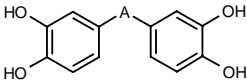
269586

4-[2-[3-[3,4-Bis(glycyloxy)phenyl]propoxy]ethyl]phenol

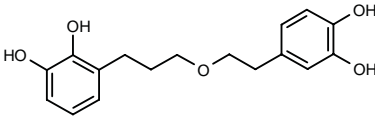


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SOURCE – Tsumura.

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SEVELAMER HYDROCHLORIDE⁺

222461

Allylamine polymer with 1-chloro-2,3-epoxypropane hydrochloride

Poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride

GT16-026A

PB-94

ACTION – Nonabsorbed polymeric phosphate binder for oral administration, designed to bind and remove dietary phosphorus in the gastrointestinal tract and eliminate it through normal digestive processes.

INDICATION – Reduction of serum phosphorus in patients with end-stage renal disease.

PRESENTATION – Capsules, 403 mg of sevelamer hydrochloride on an anhydrous base.

PROPRIETARY NAME – *RenaGel* (US).

SOURCES – GelTex; Genzyme.

REFERENCES

- Burke, S.K. et al. *RenaGel®: a novel calcium- and aluminium-free phosphate binder, inhibits phosphate absorption in normal volunteers*. *Nephrol Dial Transplant* 1997, 12(8): 1640.
- Chertow, G.M. et al. *Poly[allylamine hydrochloride] (RenaGel): A noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure*. *Am J Kidney Dis* 1997, 29(1): 66.
- Chertow, G.M. et al. *Poly[allylamine] hydrochloride (RenaGel®) [RG] with and without supplemental calcium [C] for hyperphosphatemia [HP] in ESRD*. *J Am Soc Nephrol* 1997, Abst A2559.
- Chugai Pharmaceutical develops a hyperphosphatemia agent with a U.S. bioventure company. *Nikkei Sangyo Shinbun* 1995, October 13.
- European marketing application submitted for *RenaGel*. *Prous Science Daily Essentials* 1998, July 10.
- FDA accepts *RenaGel* NDA for filing. *Prous Science Daily Essentials* 1998, Jan 22.
- GelTex announces positive preliminary phase IIc results for *RenaGel®* phosphate binder. Company also receives second patent on cholesterol reducing polymers. *GelTex Pharmaceuticals, Inc. Press Release* 1997, April 8.
- GelTex Pharmaceuticals begins phase III clinical trials of *RenaGel™* phosphate binder. *GelTex Pharmaceuticals, Inc. Press Release* 1996, June 17.
- GelTex Pharmaceuticals raises additional \$3,750,000 through exercise of over-allotment option. *GelTex Pharmaceuticals, Inc. Press Release* 1995, Nov 16.
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- GelTex Pharmaceuticals, Inc. Hambrech & Quist LLC Equity Report 1996, May 15.
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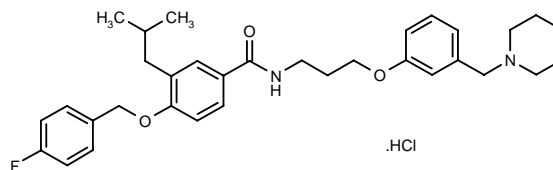
⁺Drug Data Report 1998, 020(04): 0321.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

268994

4-(4-Fluorobenzyloxy)-3-isobutyl-N-[3-[3-(1-piperidylmethyl)phenoxy]propyl]benzamide hydrochloride



C33 H41 F N2 O3 . HCl; Mol wt: 569.1568

ACTION – Antiulcer agent with high antisecretory activity (104.0% inhibition of acid secretion at 10 μ M in isolated rabbit gastric fundus gland suspensions) and anti-*Helicobacter pylori* activity (MIC = 3.13-12.5 μ g/ml against *H. pylori* NCTC 11637). *In vivo*, it inhibited ulcer formation by 55% in a water-immersion stress-induced ulcer test in rats at 100 mg/kg p.o. Compound exhibited no cytotoxic effects in rabbit gastric corpus mucosa homogenates at a concentration of 100 μ M. Another compound from this series of benzamide derivatives is:

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222461

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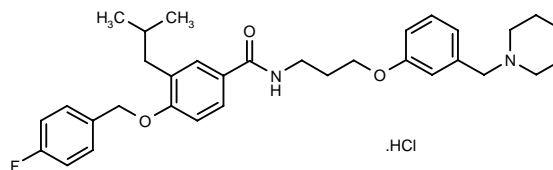
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

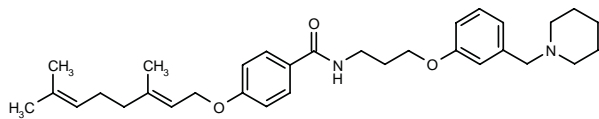
268994

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268995: C32 H44 N2 O3

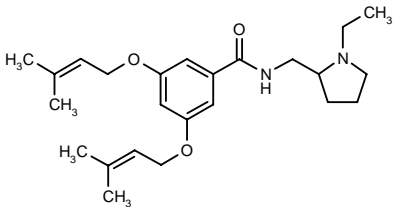
SOURCE – Shiseido.

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1. Nishino, C. and Kojima, N. (Shiseido Co. Ltd.) *Benzamide deriv., anti-ulcer drug, and antibacterial drug.* EP 869124, JP 98279570.

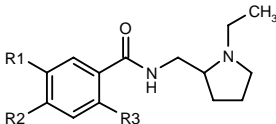
269070

N-(1-Ethylpyrrolidin-2-ylmethyl)-3,5-bis(3-methyl-2-butenyloxy)benzamide

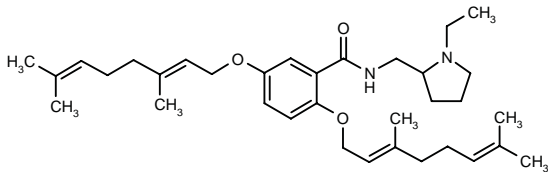


C24 H36 N2 O3; Mol wt: 400.5594

ACTION – Antiulcer agent proven active *in vivo* against restraint/water-immersion stress-induced ulcers in rats (81% inhibition at 100 mg/kg p.o.) and to exert marked gastric antisecretory activity *in vitro* in rabbit gastric fundus gland preparations (100.3% inhibition at 10 μ M). No toxicity or mortality was observed in mice following a single dose of 2000 mg/kg p.o. Within this series of pyrrolidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269071	H	(Z)-OCH2CH=C(Me)-CH2CH2CH=C(Me)2	H	C ₂₄ H ₃₆ N ₂ O ₂
269072	H	OCH2CH=C(Me)2	OCH2CH=C(Me)2	C ₂₄ H ₃₆ N ₂ O ₃
269073	OMe	(E)-OCH2CH=C(Me)-CH2CH2CH=C(Me)2	H	C ₂₅ H ₃₈ N ₂ O ₃



270166: C34 H52 N2 O3

Certain compounds within the scope of the invention also exert anti-*Helicobacter pylori* activity.

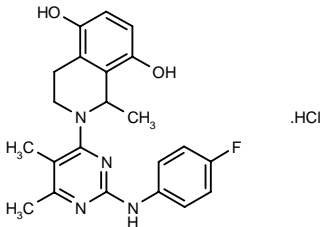
SOURCE – Shiseido.

REFERENCES

1. Nishino, C. and Uetake, T (Shiseido Co. Ltd.) *Pyrrolidine deriv., anti-ulcer drug, and antibacterial drug.* EP 869118, JP 98279556.

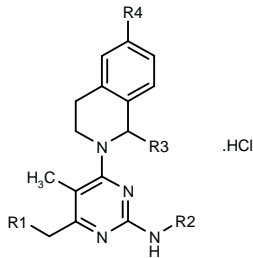
269538

N-[4-(5,8-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-5,6-dimethylpyrimidin-2-yl]-*N*-(4-fluorophenyl)amine hydrochloride



C22 H23 F N4 O2 . HCl; Mol wt: 430.9086

ACTION – Antiulcer agent, a reversible proton pump (H⁺/K⁺-ATPase) inhibitor that is expected to induce less side effects than irreversible inhibitors such as omeprazole. *In vitro*, it was found to inhibit H⁺/K⁺-ATPase activity with an IC₅₀ value of 0.18 μ M, being about 62-fold more potent than omeprazole (IC₅₀ = 11.10 μ M). Other compounds within this series of substituted pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
269539	H	4-Me-2-thiazolyl	H	H	C ₁₉ H ₂₁ N ₅ S.HCl
269540	OH	2-Me-Ph	Me	H	C ₂₃ H ₂₈ N ₄ O.HCl
269541	H	4-F-Ph	Me	OH	C ₂₂ H ₂₃ FN ₄ O.HCl

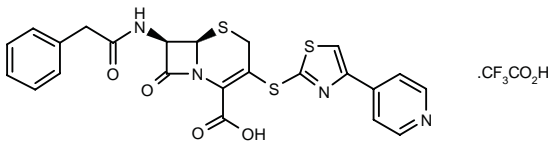
SOURCE – Yuhan.

REFERENCES

1. Lee, J.W. et al. (Yuhan Corp.) *Novel pyrimidine derivs. and processes for the preparation thereof.* WO 9843968.

269790

(6*R*,7*R*)-7-(2-Phenylacetamido)-3-[4-(4-pyridyl)thiazol-2-ylsulfanyl]-3-cephem-4-carboxylic acid trifluoroacetate



C23 H18 N4 O4 S3 . C2 H F3 O2; Mol wt: 624.6391

ACTION – Antiulcer agent, a cephem compound with potent activity against *Helicobacter pylori* (MIC = 0.006 µg/ml or less against *H. pylori* strains NTC11637 and TN2; MIC = 0.05 µg/ml for clarithromycin). Activity was also demonstrated *in vivo* in gerbils infected with *H. pylori* TN85GF4, where it reduced bacterial count (log CFU) from 6.30 ± 0.27 in the control group to 3.94 ± 1.42 at 3 mg/kg b.i.d. p.o. x 7 days (3.50 ± 2.57 for clarithromycin at 30 mg/kg b.i.d. p.o. x 7 days).

SOURCE – Takeda.

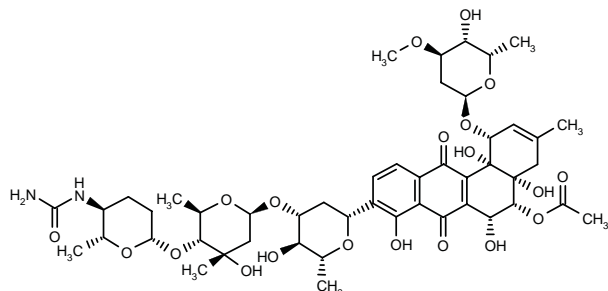
REFERENCES

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P371A1

267859

[1*R*-(1α,4α,5α,6α,12bα)]-5-Acetoxy-9-[2,6-dideoxy-3-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(2,3,4,6-tetradecoxy-4-ureido-β-*D*-glucopyranosyl)-β-*D*-allopyranosyl]-β-*D*-glucopyranosyloxy]-1-(2,6-dideoxy-3-*O*-methyl-α-*L*-idopyranosyloxy)-4a,6,8,12b-tetrahydroxy-3-methyl-1,4,4a,5,6,7,12,12b-octahydrobenzo[*a*]anthracene-7,12-dione



C48 H66 N2 O20; Mol wt: 991.0434

Orange powder.

ACTION – Compound extracted from *Streptomyces* sp. P371, with both antagastin and gastric mucosal protective activity. Compound significantly reduced pentagastrin-stimulated gastric acid secretion in rats (61% at 10 mg/kg i.p.), but had no effect against histamine- and carbachol-induced secretion. It also protected against HCl/ethanol (52.6, 81.6 and 83.6% inhibition, respectively, at 1, 3 and 10 mg/kg i.p.) and indomethacin-induced gastric damage in rats (57.0, 64.9 and 72.8% inhibition, respectively).

SOURCE – Japan Tobacco.

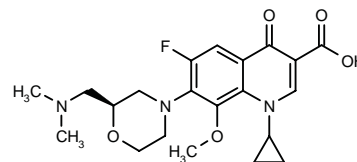
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1. Uesato, S. et al. *Novel angucycline compound with both antagastin- and gastric mucosal protective-activities*. Bioorg Med Chem Lett 1998, 8(15): 1969.

Y-34867

267927

(-)-1-Cyclopropyl-7-[2(*S*)-(dimethylaminomethyl)-morpholin-4-yl]-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid



C21 H26 F N3 O5; Mol wt: 419.4504

M.p. 144-6 °C.

ACTION – Quinolone antibacterial agent with high photostability, useful for eradicating *Helicobacter pylori*. Compound shows comparable or superior *in vitro* activity to amoxicillin and clarithromycin (MIC₉₀ = 0.05 µg/ml vs. 0.05 and 0.10 µg/ml, respectively). *In vivo*, in Mongolian gerbil and mouse *H. pylori* infection models, compound administered orally at doses of 1-3 mg/kg b.i.d. for 7 days exhibited a therapeutic effect superior to amoxicillin and clarithromycin. In combination with famotidine (0.3 mg/kg p.o. + 100 mg/kg s.c.), the compound showed a potent synergistic effect in *H. pylori*-infected Mongolian gerbils.

SOURCE – Yoshitomi.

REFERENCES

1. Yokota, K. et al. (Yoshitomi Pharmaceutical Industries, Ltd.) *Pyridonecarboxylic acid cpds*. JP 91007283.
2. Sakurai, N. et al. *Synthesis and anti-Helicobacter pylori activity of Y-34867, a new 7-morpholinoquinolone*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abstr F-85.
3. Sakurai, N. et al. *Synthesis and structure-activity relationships of 7-(2-aminoalkyl)morpholinoquinolones as anti-Helicobacter pylori agents*. Bioorg Med Chem Lett 1998, 8(16): 2185.

INFLAMMATORY BOWEL DISEASE THERAPY

INFLIXIMAB

Prop INN

198460

Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light chain, dimer

cA2

CenTNFTM,+

TA-650

AvakineTM (former name)

ACTION – Recombinantly produced chimeric mouse-human monoclonal antibody that binds specifically to human tumor necrosis factor α (TNF-α), inhibiting TNF-α binding to its receptors and neutralizing its biological activity; it does not neutralize the effects of the related cytokine TNF-β (lymphotoxin α).

INDICATION – Treatment of moderately to severely active Crohn’s disease for the reduction of the signs and symptoms in patients who have an inadequate response to conventional therapy.

PRESENTATION – Single-use vials containing lyophilized powder for i.v. infusion following reconstitution, 100 mg.

PROPRIETARY NAME – *Remicade* (US).

SOURCE – Centocor.

RECENT REFERENCES

1. Clark, M.A. et al. *Effect of a TNF monoclonal antibody on the measurement of serum TNF in severe sepsis*. Cytokine 1997, 9(11): Abst 44.

2. Emmell, E. et al. *Evaluation of the therapeutic effect of chimeric anti-human TNF monoclonal antibody (cA2) in combination with methotrexate in Tg197 arthritic mice*. 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst W27.

3. Emmell, E. et al. *Evaluation of the therapeutic effect of chimeric anti-human TNF monoclonal antibody (cA2) on different stages of polyarthritis in Tg197 mice*. 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst W26.

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16. *Centocor announces results from studies of Crohn’s disease therapy*. Centocor, Inc. Press Release 1997, May 12.

17. *Centocor receives complete review letter for infliximab*. Prous Science Daily Essentials 1998, July 2.

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19. *FDA advisory committee recommends approval of Avakine for Crohn’s disease*. Prous Science Daily Essentials 19980, May 29.

20. *FDA advisory committee will meet to discuss Avakine NDA*. Prous Science Daily Essentials 1998, April 28.

21. *FDA approves first treatment for Crohn’s disease*. Prous Science Daily Essentials 1998, Aug 27.

22. *Infliximab development status*. Centocor, Inc. Company Communication 1998, Oct 6.

23. *Priority review status granted for Avakine*. Prous Science Daily Essentials 1998, Feb 26.

24. *Promising clinical results reported for Avakine*. Prous Science Daily Essentials 1997, Nov 13.

25. *Remicade™ - Infliximab for iv injection*. Centocor, Inc. Product Fact Sheet 1998, Aug 19.

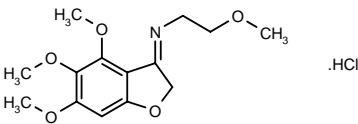
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*Drug Data Report 1993, 015(11): 0995.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

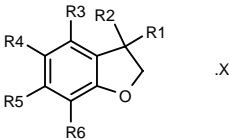
263800

4,5,6-Trimethoxy-3-(2-methoxyethylimino)-2,3-dihydrobenzofuran hydrochloride



C14 H19 N O5 . HCl; Mol wt: 317.7670

ACTION – Hepatoprotectant proven active in a D-galactosamine-induced hepatopathy model in rats, where it produced a 78% reduction in both plasma AST and plasma ALT levels at 30 mg/kg p.o. x 4 days. A representative compound from a series of 2,3-dihydrobenzofuran derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
267353	-N(i-Bu)-		OMe	H	OMe	H	HCl	C ₁₄ H ₁₉ NO ₃ .HCl
267354	-N(i-Bu)-		OMe	OMe	OMe	H	HCl	C ₁₅ H ₂₁ NO ₄ .HCl
267355	NHOMe	H	OMe	H	OMe	H	HCl	C ₁₁ H ₁₅ NO ₄ .HCl
267356	NHSO ₂ Me	H	H	H	OMe	OMe		C ₁₁ H ₁₅ NO ₅ S
267357	NHSO ₂ Ph	H	H	H	OMe	OMe		C ₁₆ H ₁₇ NO ₅ S
267358	NHSO ₂ Me	H	OMe	OH	OMe	H		C ₁₁ H ₁₅ NO ₆ S
267359	NHSO ₂ Me	H	OMe	OMe	H	OMe		C ₁₂ H ₁₇ NO ₆ S

SOURCE – Dainippon Pharmaceutical.

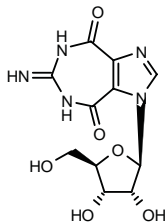
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NABI-3700.001^{1,2}

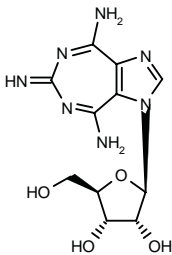
268291

(2*R*,3*R*,4*S*,5*R*)-1-[3,4-Dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-imino-6,7-dihydroimidazo[4,5-*e*]-[1,3]diazepine-4,8(1*H*,5*H*)-dione

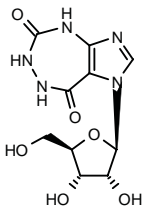


C11 H13 N5 O6; Mol wt: 311.2527

ACTION – Antiviral nucleoside analogue, with potent activity against hepatitis B virus (HBV). It decreases HBV DNA and the production of intracellular HBV replicative intermediates in transfected 2.2.15 hepatoma cells with EC₅₀s of 0.17 and 0.6 μM, respectively, with no effect against HIV or herpesviruses and low cytotoxicity (CC₅₀ = 2.4 mM and > 100 μM, respectively, in 2.2.15 and rapidly growing HFF cells). A candidate for further development against HBV infections in humans. Other related compounds are:



Nabi-3700.002¹ [268292]: C11 H15 N7 O4



Nabi-3700.003¹ [268293]: C10 H13 N5 O6

SOURCES – University of Maryland, Baltimore, MD (US); Nabi.

REFERENCES

1. Sood, R.K. et al. *A ring expanded nucleoside analog with potent activity against hepatitis B virus (HBV) and low cellular toxicity*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-152.

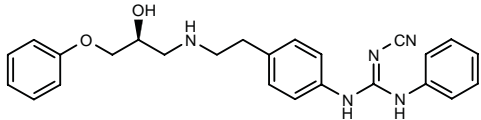
2. *Nabi licenses technology for development of antiviral drug*. Prous Science Daily Essentials 1998, June 24.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

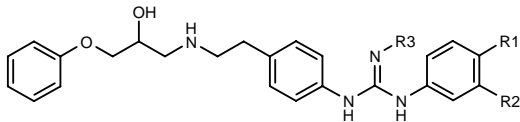
265914

*N*²-Cyano-*N*¹-[4-[2-[2(*S*)-hydroxy-3-phenoxypropyl-amino]ethyl]phenyl]-*N*³-phenylguanidine



C25 H27 N5 O2; Mol wt: 429.5213

ACTION – Antidiabetic agent that stimulates insulin secretion and potentiates insulin sensitivity, a representative compound from a series of guanidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Isomer	Formula
266616	OMe	H	CONH2	S	C ₂₆ H ₃₃ Cl ₂ N ₅ O ₄
266617	H	H	NO2		C ₂₄ H ₂₇ N ₅ O ₄
266618	OMe	H	NO2		C ₂₅ H ₂₉ N ₅ O ₅
266619	OMe	H	SO2NH2		C ₂₅ H ₃₁ N ₅ O ₅ S
266620	OH	H	CONH2		C ₂₅ H ₂₉ N ₅ O ₄
266621	CO2Et	H	CONH2		C ₂₈ H ₃₃ N ₅ O ₅
266622	-OCH2O-		CONH2		C ₂₆ H ₂₉ N ₅ O ₅

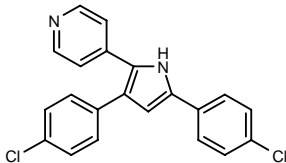
SOURCE – Yamanouchi.

REFERENCES

1. Maruyama, R. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel guanidine derivs. or salts thereof*. JP 98158233.

267209

3,5-Bis(4-chlorophenyl)-2-(4-pyridyl)-1*H*-pyrrole

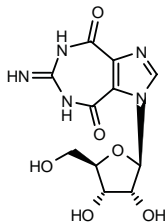


C21 H14 Cl2 N2; Mol wt: 365.2616

NABI-3700.001^{1,2}

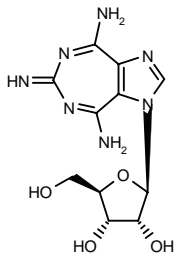
268291

(2*R*,3*R*,4*S*,5*R*)-1-[3,4-Dihydroxy-5-(hydroxymethyl)-tetrahydro-2-furanyl]-6-imino-6,7-dihydroimidazo[4,5-*e*]-[1,3]diazepine-4,8(1*H*,5*H*)-dione

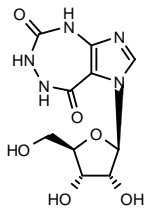


C11 H13 N5 O6; Mol wt: 311.2527

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SOURCES – University of Maryland, Baltimore, MD (US); Nabi.

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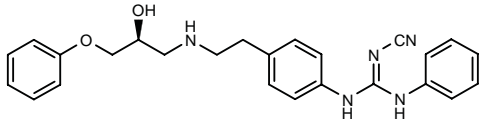
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

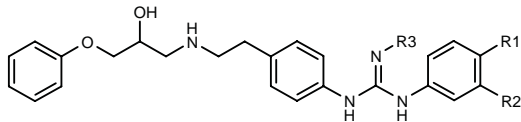
265914

*N*²-Cyano-*N*¹-[4-[2-[2(*S*)-hydroxy-3-phenoxypropyl-amino]ethyl]phenyl]-*N*³-phenylguanidine



C25 H27 N5 O2; Mol wt: 429.5213

ACTION – Antidiabetic agent that stimulates insulin secretion and potentiates insulin sensitivity, a representative compound from a series of guanidine derivatives, wherein the following are also included:



Compound	R1	R2	R3	Isomer	Formula
266616	OMe	H	CONH2	S	C ₂₆ H ₃₃ Cl ₂ N ₅ O ₄
266617	H	H	NO2		C ₂₄ H ₂₇ N ₅ O ₄
266618	OMe	H	NO2		C ₂₅ H ₂₉ N ₅ O ₅
266619	OMe	H	SO2NH2		C ₂₅ H ₃₁ N ₅ O ₅ S
266620	OH	H	CONH2		C ₂₅ H ₂₉ N ₅ O ₄
266621	CO2Et	H	CONH2		C ₂₈ H ₃₃ N ₅ O ₅
266622	-OCH2O-		CONH2		C ₂₆ H ₂₉ N ₅ O ₅

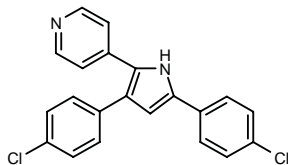
SOURCE – Yamanouchi.

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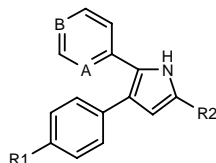
267209

3,5-Bis(4-chlorophenyl)-2-(4-pyridyl)-1*H*-pyrrole



C21 H14 Cl2 N2; Mol wt: 365.2616

ACTION – A glucagon receptor antagonist ($IC_{50} < 2 \mu M$) and inhibitor of proinflammatory cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor (TNF- α). Claimed for the treatment of diabetes, septic shock, bone resorption disorders, graft-versus-host reaction, atherosclerosis, arthritis, gout, psoriasis, adult respiratory distress syndrome, asthma, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, inflammatory bowel disease, cachexia or viral infections. Other specifically claimed compounds from this series of substituted pyridyl pyrrole derivatives include the following:



Compound	R1	R2	A	B	Formula
267210	F	4-Cl-Ph	N	CH	C ₂₁ H ₁₄ ClFN ₂
267211	F	4-(MeSO)-Ph	CH	N	C ₂₂ H ₁₇ FN ₂ OS
267212	F	4-(MeNH)-Ph	CH	N	C ₂₂ H ₁₈ FN ₃
267213	F	4-NH ₂ -Ph	CH	N	C ₂₁ H ₁₆ FN ₃
267214	F	3-NH ₂ -Ph	CH	N	C ₂₁ H ₁₆ FN ₃
267215	F	2-NH ₂ -Ph	CH	N	C ₂₁ H ₁₆ FN ₃
267216	F	1-Me-4-Pip	CH	N	C ₂₁ H ₂₂ FN ₃
267217	Ph	4-Cl-Ph	CH	N	C ₂₇ H ₁₉ ClN ₂
267218	F	4-(PhSO)-Ph	CH	N	C ₂₇ H ₁₉ FN ₂ OS

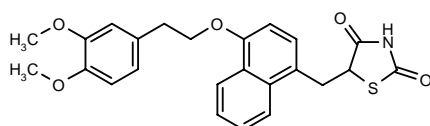
SOURCE – Merck & Co.

REFERENCES

1. Chang, L.L. et al. (Merck & Co., Inc.) *Subst. pyridyl pyrroles, compsns. containing such cpds. and methods of use*. US 5776954.

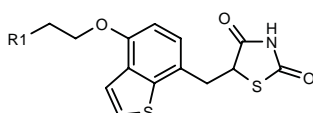
269791

5-[4-[2-(3,4-Dimethoxyphenyl)ethoxy]naphthalen-1-ylmethyl]thiazolidine-2,4-dione

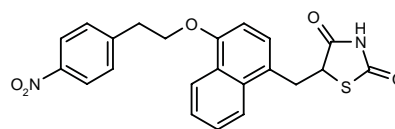


C₂₄ H₂₃ N O₅ S; Mol wt: 437.5137

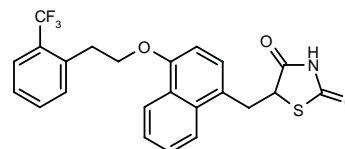
ACTION – Orally active antidiabetic agent proven to decrease blood glucose levels by 94% in *ob/ob* mice at 80 mg/kg/day p.o. x 3 days. Other exemplified compounds from this series of thiazolidinediones include the following:



Compound	R1	Formula
269794	4-F-Ph	C ₂₀ H ₁₆ FN ₃ S ₂
269795	cyclohexyl-CH ₂	C ₂₁ H ₂₅ NO ₃ S ₂
269796	(CH ₂) ₄ Ph	C ₂₄ H ₂₅ NO ₃ S ₂
269797	4-MeO-PhCH ₂ CH ₂	C ₂₃ H ₂₃ NO ₄ S ₂



269792: C₂₂ H₁₈ N₂ O₅ S



269793: C₂₃ H₁₈ F₃ N O₃ S

SOURCE – Roche.

REFERENCES

1. Wolff, H.-P. et al. (Boehringer Mannheim GmbH) *New thiazolidinediones, method for the production thereof, and medicaments containing the same*. WO 9842691.

LISPRO MIX25

266377

Insulin mixture containing 25% insulin lispro and 75% insulin lispro–protamine suspension (NPL 75%)

MIX25

ACTION – Insulin mixture containing 25% insulin lispro⁺ and 75% NPL (a sustained-release insulin lispro–protamine suspension), proven to reduce the postprandial increase in serum glucose compared to human 30/70 insulin (30% regular insulin, 70% NPH) or NPH insulin, while providing similar glycemic control at other times in patients with type II diabetes. It has the advantage of being effective when given immediately prior to meals.

SOURCE – University of Helsinki, Helsinki (FI).

REFERENCES

1. Koivisto, V.A. et al. *Lispro MIX25 reduces postprandial glucose compared to human insulin 30/70 and NPH in NIDDM patients*. 34th Annu Meet Eur Assoc Study Diabetes (Sept 8-12, Barcelona) 1998, Abst 953.

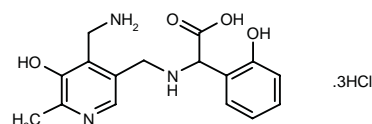
2. Roach, P. et al. *Improved postprandial glycemia during treatment with a lispro/intermediate-acting insulin mixture, MIX25*. 34th Annu Meet Eur Assoc Study Diabetes (Sept 8-12, Barcelona) 1998, Abst 943.

⁺Drug Data Rep 1996, 018(04): 0350.

TREATMENT OF DIABETIC COMPLICATIONS

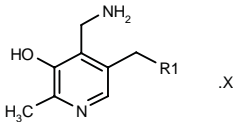
265916

2-[4-(Aminomethyl)-5-hydroxy-6-methylpyridin-3-ylmethylamino]-2-(2-hydroxyphenyl)acetic acid trihydrochloride



C₁₆ H₁₉ N₃ O₄ . 3HCl; Mol wt: 426.7258

ACTION – An inhibitor of the Maillard reaction, a representative compound from a series of 5-aminoalkyl-4-aminomethyl-3-hydroxypyridines, wherein the following are also included:



Compound	R1	X	Formula
266638	4-PhCH2-1-Piz	4HCl	C ₁₉ H ₂₆ N ₄ O ₄ ·4HCl
266639	NHPr	3HCl	C ₁₁ H ₁₉ N ₃ O ₃ ·3HCl
266640	N(Me)CH2Ph	3HCl	C ₁₆ H ₂₁ N ₃ O ₃ ·3HCl
266641	4-OH-PhNH	3HCl	C ₁₄ H ₁₇ N ₃ O ₂ ·3HCl

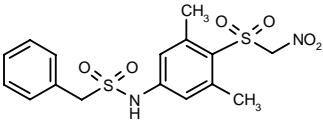
SOURCE – Kissei.

REFERENCES

1. Iyobe, R. et al. (Kissei Pharmaceutical Co., Ltd.) 5-Aminoalkyl-4-aminomethyl-3-hydroxypyridine derivs. and Maillard reaction inhibitors containing them. JP 98158244.

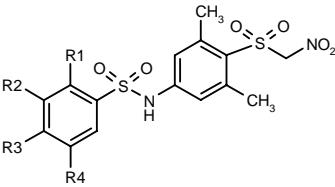
268867

N-[3,5-Dimethyl-4-(nitromethylsulfonyl)phenyl]benzyl-sulfonamide



C16 H18 N2 O6 S2; Mol wt: 398.4582

ACTION – Symptomatic antidiabetic agent that acts by virtue of its aldose reductase-inhibitory activity (IC₅₀ = 6 nM against rat lens enzyme). *In vivo*, it produced complete protection against accumulation of sorbitol in the sciatic nerve of streptozotocin-diabetic rats at a dose of 5 mg/kg p.o. Within this series of specifically claimed nitromethylthiobenzene derivatives, the following are also included:



Compound	R1	R2	R3	R4	Formula
268868	H	H	H	H	C ₁₅ H ₁₆ N ₂ O ₆ S ₂
268869	H	H	F	F	C ₁₅ H ₁₄ F ₂ N ₂ O ₆ S ₂
268870	H	H	H	Br	C ₁₅ H ₁₅ BrN ₂ O ₆ S ₂
268871	CF3	H	H	H	C ₁₆ H ₁₅ F ₃ N ₂ O ₆ S ₂
268872	H	H	F	H	C ₁₅ H ₁₅ FN ₂ O ₆ S ₂
268873	H	H	H	F	C ₁₅ H ₁₅ FN ₂ O ₆ S ₂
268874	F	F	H	H	C ₁₅ H ₁₄ F ₂ N ₂ O ₆ S ₂
268875	H	F	H	F	C ₁₅ H ₁₄ F ₂ N ₂ O ₆ S ₂
268876	F	H	H	H	C ₁₅ H ₁₅ FN ₂ O ₆ S ₂

SOURCE – Merck KGaA.

REFERENCES

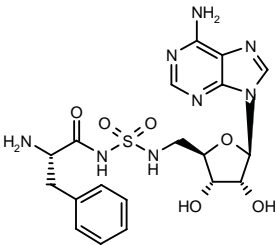
1. Collonges, F. et al. (Merck Patent GmbH) Nitromethylthiobenzene derivs. as inhibitors of aldose reductase. WO 9828265.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

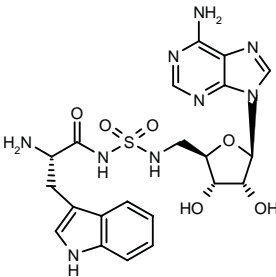
269233

5'-Deoxy-5'-(N'-L-phenylalanylsulfamido)adenosine



C19 H24 N8 O6 S; Mol wt: 492.5146

ACTION – Agent for the topical treatment of hyperproliferative disorders, particularly psoriasis, a potent inhibitor of the proliferation of human epidermoid carcinoma cells (IC₅₀ = 0.53 μM) and normal skin fibroblast cells (IC₅₀ = 5.58 μM). It shows good penetration of the target tissue, the epidermis, as demonstrated in intact human cadaver skin. LD₅₀ = 44 mg/kg i.p. in mice. Another representative compound within this series of aminoacyl sulfamide derivatives is:



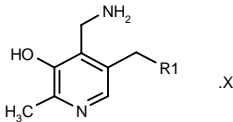
270170: C21 H25 N9 O6 S

SOURCE – Cubist.

REFERENCES

1. Hill, J.M. and Kluge, A.F. (Cubist Pharmaceuticals, Inc.) Aminoacyl sulfamides for the treatment of hyperproliferative disorders. US 5824657, WO 9841215.

ACTION – An inhibitor of the Maillard reaction, a representative compound from a series of 5-aminoalkyl-4-aminomethyl-3-hydroxypyridines, wherein the following are also included:



Compound	R1	X	Formula
266638	4-PhCH2-1-Piz	4HCl	C ₁₉ H ₂₆ N ₄ O ₄ ·4HCl
266639	NHPr	3HCl	C ₁₁ H ₁₉ N ₃ O ₃ ·3HCl
266640	N(Me)CH2Ph	3HCl	C ₁₆ H ₂₁ N ₃ O ₃ ·3HCl
266641	4-OH-PhNH	3HCl	C ₁₄ H ₁₇ N ₃ O ₂ ·3HCl

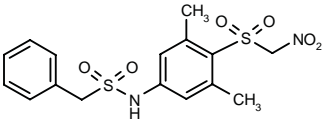
SOURCE – Kissei.

REFERENCES

1. Iyobe, R. et al. (Kissei Pharmaceutical Co., Ltd.) 5-Aminoalkyl-4-aminomethyl-3-hydroxypyridine derivs. and Maillard reaction inhibitors containing them. JP 98158244.

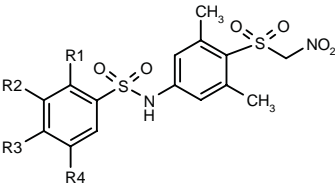
268867

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C16 H18 N2 O6 S2; Mol wt: 398.4582

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Compound	R1	R2	R3	R4	Formula
268868	H	H	H	H	C ₁₅ H ₁₆ N ₂ O ₆ S ₂
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268870	H	H	H	Br	C ₁₅ H ₁₅ BrN ₂ O ₆ S ₂
268871	CF3	H	H	H	C ₁₆ H ₁₅ F ₃ N ₂ O ₆ S ₂
268872	H	H	F	H	C ₁₅ H ₁₅ FN ₂ O ₆ S ₂
268873	H	H	H	F	C ₁₅ H ₁₅ FN ₂ O ₆ S ₂
268874	F	F	H	H	C ₁₅ H ₁₄ F ₂ N ₂ O ₆ S ₂
268875	H	F	H	F	C ₁₅ H ₁₄ F ₂ N ₂ O ₆ S ₂
268876	F	H	H	H	C ₁₅ H ₁₅ FN ₂ O ₆ S ₂

SOURCE – Merck KGaA.

REFERENCES

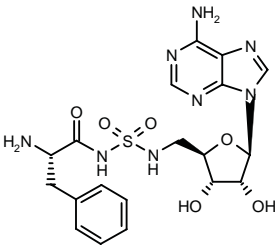
1. Collonges, F. et al. (Merck Patent GmbH) Nitromethylthiobenzene derivs. as inhibitors of aldose reductase. WO 9828265.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

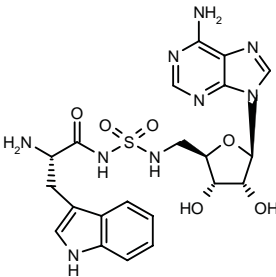
269233

5'-Deoxy-5'-(N'-L-phenylalanylsulfamido)adenosine



C19 H24 N8 O6 S; Mol wt: 492.5146

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270170: C21 H25 N9 O6 S

SOURCE – Cubist.

REFERENCES

1. Hill, J.M. and Kluge, A.F. (Cubist Pharmaceuticals, Inc.) Aminoacyl sulfamides for the treatment of hyperproliferative disorders. US 5824657, WO 9841215.

MISCELLANEOUS DERMATOLOGIC DRUGS

THALIDOMIDE⁺

Rec INN; BAN; USAN

091361

2-(2,6-Dioxopiperidin-3-yl)-2,3-dihydro-1*H*-isoindole-1,3-dione

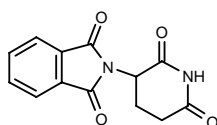
N-(2,6-Dioxopiperidin-3-yl)phthalimide

α -(*N*-Phthalimido)glutarimide

K-17

NSC-66847

SynovirTM



C13 H10 N2 O4; Mol wt: 258.2320

ACTION – Immunomodulating agent whose spectrum and mechanism of action have not been fully established, although data from *in vitro* and preliminary clinical trials indicate that its activity may be related to suppression of excessive tumor necrosis factor- α (TNF- α) production and downmodulation of selected cell-surface adhesion molecules involved in leukocyte migration.

First introduced in Europe in the 1950s as a sedative and withdrawn in 1962 when found to cause birth defects, it is also undergoing clinical studies for a number of other indications.

INDICATION – Treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum.

PRESENTATION – Capsules, 50 mg.

PROPRIETARY NAME – Thalomid (US).

SOURCE – Celgene.

RECENT RELATED REFERENCES

- Kaplan, G. and Sampaio, E.P. (Rockefeller University) *Method for controlling abnormal concentration of TNF- α in human tissues*. US 5385901, WO 9214455.
- Afghani, B. and Fujiyama, D. *In vitro effect of thalidomide on TNF- α concentrations after infection of monocytes of HIV-infected patients with mycobacteria*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abstr 1-30.
- Dibbs, Z.I. et al. *Thalidomide and thalidomide analogs suppress TNF α secretion by myocytes*. Circulation 1998, 98(17, Suppl.): Abstr 1284.
- Lee, J.B. and Koblenzer, P.S. *Disfiguring cutaneous manifestation of sarcoidosis treated with thalidomide: A case report*. J Am Acad Dermatol 1998, 39(5, Part 2): 835.
- Rowland, T.L. et al. *Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells*. Immunopharmacology 1998, 40(1): 11.
- Teo, S. et al. *A single dose 3-way crossover bioequivalence study of 2 oral formulations of thalidomide and the relative bioequivalence with and without food in healthy volunteers*. J Clin Pharmacol 1998, 38(9): Abstr 617.
- Celgene acquires EntreMed rights to thalidomide. Prous Science Daily Essentials 1998, Dec 14.

8. Celgene cleared to market Thalomid in U.S. Prous Science Daily Essentials 1998, July 20.

9. Thalidomide new launch. Celgene Corp. Company Communication 1998, Oct 5.

10. Thalomid now available for prescribing in U.S. Prous Science Daily Essentials 1998, Oct 2.

MONOGRAPH – Sommer, C. *Thalidomide as a blocker of TNF production*. Drugs Fut 1999, 024(01): in preparation.

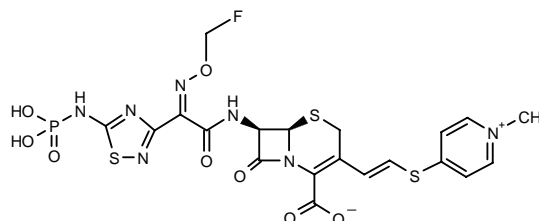
⁺Drug Data Report 1995, 017(05): 0468 and 0482.

ANTIINFECTIVE THERAPY

β -LACTAM ANTIBIOTICS

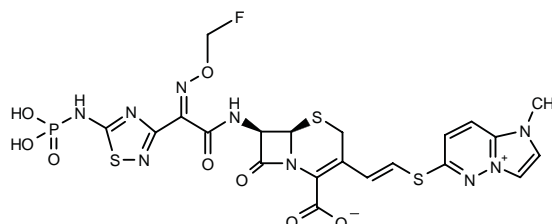
269773

(6*R*,7*R*)-7-[2(*Z*)-(Fluoromethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[2(*E*)-(1-methylpyridinium-4-ylsulfanyl)vinyl]-3-cephem-4-carboxylate



C20 H19 F N7 O8 P S3; Mol wt: 631.5811

ACTION – Cephem antibiotic from a series of phosphonocephem derivatives, wherein the following is also included:



269774: C21 H19 F N9 O8 P S3

SOURCE – Takeda.

REFERENCES

- Ishikawa, T. et al. (Takeda Chemical Industries, Ltd.) *Phosphonocephem derivs*. JP 98265488.

MISCELLANEOUS DERMATOLOGIC DRUGS

THALIDOMIDE⁺

Rec INN; BAN; USAN

091361

2-(2,6-Dioxopiperidin-3-yl)-2,3-dihydro-1*H*-isoindole-1,3-dione

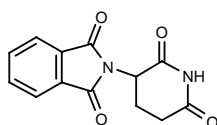
N-(2,6-Dioxopiperidin-3-yl)phthalimide

α -(*N*-Phthalimido)glutarimide

K-17

NSC-66847

SynovirTM



C13 H10 N2 O4; Mol wt: 258.2320

ACTION – Immunomodulating agent whose spectrum and mechanism of action have not been fully established, although data from *in vitro* and preliminary clinical trials indicate that its activity may be related to suppression of excessive tumor necrosis factor- α (TNF- α) production and downmodulation of selected cell-surface adhesion molecules involved in leukocyte migration.

First introduced in Europe in the 1950s as a sedative and withdrawn in 1962 when found to cause birth defects, it is also undergoing clinical studies for a number of other indications.

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PRESENTATION – Capsules, 50 mg.

PROPRIETARY NAME – Thalomid (US).

SOURCE – Celgene.

RECENT RELATED REFERENCES

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- Afghani, B. and Fujiyama, D. *In vitro effect of thalidomide on TNF- α concentrations after infection of monocytes of HIV-infected patients with mycobacteria*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abstr 1-30.
- Dibbs, Z.I. et al. *Thalidomide and thalidomide analogs suppress TNF α secretion by myocytes*. Circulation 1998, 98(17, Suppl.): Abstr 1284.
- Lee, J.B. and Koblenzer, P.S. *Disfiguring cutaneous manifestation of sarcoidosis treated with thalidomide: A case report*. J Am Acad Dermatol 1998, 39(5, Part 2): 835.
- Rowland, T.L. et al. *Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells*. Immunopharmacology 1998, 40(1): 11.
- Teo, S. et al. *A single dose 3-way crossover bioequivalence study of 2 oral formulations of thalidomide and the relative bioequivalence with and without food in healthy volunteers*. J Clin Pharmacol 1998, 38(9): Abstr 617.
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8. Celgene cleared to market Thalomid in U.S. Prous Science Daily Essentials 1998, July 20.

9. Thalidomide new launch. Celgene Corp. Company Communication 1998, Oct 5.

10. Thalomid now available for prescribing in U.S. Prous Science Daily Essentials 1998, Oct 2.

MONOGRAPH – Sommer, C. *Thalidomide as a blocker of TNF production*. Drugs Fut 1999, 024(01): in preparation.

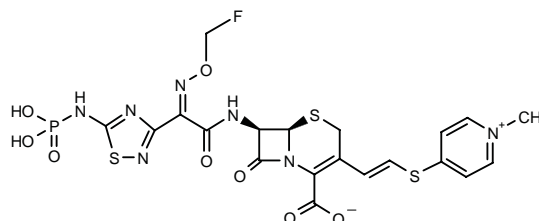
⁺Drug Data Report 1995, 017(05): 0468 and 0482.

ANTIINFECTIVE THERAPY

β -LACTAM ANTIBIOTICS

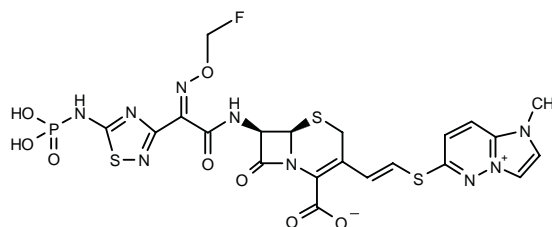
269773

(6*R*,7*R*)-7-[2(*Z*)-(Fluoromethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[2(*E*)-(1-methylpyridinium-4-ylsulfanyl)vinyl]-3-cephem-4-carboxylate



C20 H19 F N7 O8 P S3; Mol wt: 631.5811

ACTION – Cephem antibiotic from a series of phosphonocephem derivatives, wherein the following is also included:



269774: C21 H19 F N9 O8 P S3

SOURCE – Takeda.

REFERENCES

- Ishikawa, T. et al. (Takeda Chemical Industries, Ltd.) *Phosphonocephem derivs*. JP 98265488.

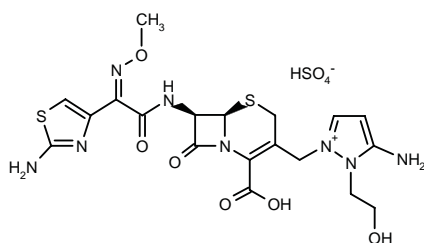
CEFOSELIS SULFATE

Rec INNM

176375

5-Amino-2-[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)-2(*Z*)-(methoxyimino)acetamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-ylmethyl]-1-(2-hydroxyethyl)-1*H*-pyrazolium sulfate (1:1)

(6*R*,7*R*)-3-[3-Amino-2-(2-hydroxyethyl)-1-pyrazoliomethyl]-7-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid hydrogen sulfate

FK-037⁺

C19 H23 N8 O6 S2 . H O4 S; Mol wt: 620.6426

ACTION – Parenteral cephalosporin antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria including *Pseudomonas* spp.

INDICATION – Treatment of a variety of moderate to severe infections caused by susceptible strains such as *Staphylococcus* or *Pseudomonas* including respiratory tract and urinary tract infections.

PRESENTATION – Vials for infusion (100 ml), 0.5 and 1 g.

PROPRIETARY NAME – Wincef (JP).

SOURCE – Fujisawa.

RECENT REFERENCES

1. Climo, M.W. et al. Comparison of the in-vitro and in-vivo efficacy of FK037, vancomycin, imipenem and nafcillin against staphylococcal species. J Antimicrob Chemother 1997, 40(1): 59.
2. Cooper, I. et al. Comparative in vitro activity of L-ofloxacin and FK037 to other agents against 10,040 fresh clinical isolates. Int J Antimicrob Agents 1996, 6(4): 201.
3. Grecka, P. et al. Antistaphylococcal activity of 4th-generation cephalosporins. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst E-169.
4. Grecka, P. et al. Comparative in vitro activity of 4th-generation cephalosporins on multiresistant enterobacteriaceae. 8th Int Cong Infect Dis (May 15-18, Boston) 1998, Abst 12.030.
5. Hatano, K. et al. The therapeutic effect of combined vancomycin and cefoselis against murine pneumonia caused by methicillin-resistant *Staphylococcus aureus* in an in vivo pharmacokinetic model. Jpn J Chemother 1996, 44(4): 213.
6. Hoshino, K. et al. Drug sensitivity of clinically isolated bacterium to various beta-lactam drugs, including cefoselis (CFSL). Jpn J Chemother 1998, 46(Suppl. A): Abst 14.
7. Ohki, H. et al. Studies on 3'-quaternary ammonium cephalosporins - IV. Synthesis and antibacterial activity of 3'-(2-alkyl-3-aminopyrazolium)cephalosporins related to FK037. Bioorg Med Chem 1997, 5(8): 1685.
8. Soejima, R. et al. A comparative study of cefoselis and ceftazidime in bacterial pneumonia. Jpn J Chemother 1996, 44(7): 509.
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10. Tympanidou, C. et al. Comparative in vitro activity of FK037 (cefoselis, FK), cefepime (CF) and ceftipime (CP) on 230 multiresistant Gram-negative isolates. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-186.

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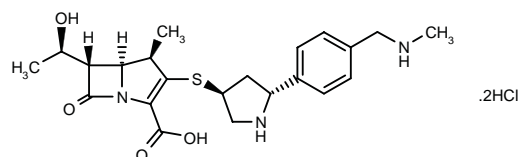
MONOGRAPH – Prous, J. et al. FK-037. Drugs Fut 1994, 019(04): 0325.

⁺Drug Data Report 1991, 013(11): 0980.

J-111225^{1,2,4-8}

268243

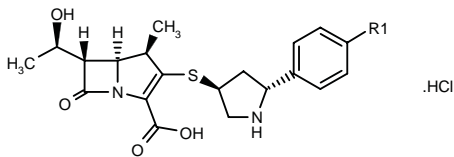
(1*R*,5*S*,6*S*)-2-[5(*R*)-[4-(Methylaminomethyl)phenyl]-pyrrolidinyl-3(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid dihydrochloride



C22 H29 N3 O4 S . 2HCl; Mol wt: 504.4759

Nonhygroscopic, colorless prisms.

ACTION – Parenteral carbapenem antibiotic with an ultrabroad spectrum against Gram-positive and Gram-negative bacteria including penicillin-resistant *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). Compound showed resistance to hydrolysis by IMP-1-metallo-β-lactamases. *In vivo*, it has good therapeutic efficacy against systemic MRSA infections in normal and immunosuppressed mice and in mouse septicemia caused by methicillin-susceptible *S. aureus*, penicillin-resistant *S. pneumoniae*, *P. aeruginosa* and *Enterobacteriaceae*. Compound is well tolerated, with little or no nephrotoxicity, hemolytic activity and low epileptogenicity, and it exhibits a favorable pharmacokinetic profile. The prototype in this series of 1β-methylcarbapenems – **J-111347** – showed potent antibacterial activity but was associated with undesirable epileptogenicity. Other related compounds considered worthy of further evaluation are:



Compound	R1	Formula
J-111347 [268131] ^{1,2,4,5,7,8}	CH2NH2	C ₂₁ H ₂₇ N ₃ O ₄ S.HCl
J-114870 [268244] ^{1,3-5,7,8}	(S)-CH(NH2)CH2CONH2	C ₂₃ H ₃₀ N ₄ O ₅ S.HCl
J-114871 [268245] ^{1,3-5,7,8}	(R)-CH(NH2)CH2CONH2	C ₂₃ H ₃₀ N ₄ O ₅ S.HCl

SOURCE – Banyu.

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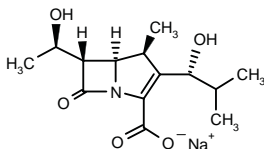
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KR-21012*

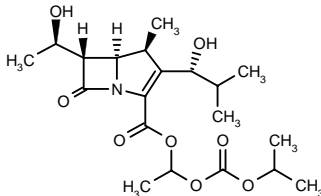
268241
253564 (as potassium salt)

(1*S*,5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[1(*R*)-hydroxy-2-methylpropyl]-1-methyl-1-carba-2-penem-3-carboxylic acid sodium salt



C14 H20 N Na O5; Mol wt: 305.3040

ACTION – Carbapenem antibiotic with broad-spectrum antibacterial activity against both Gram-positive and Gram-negative pathogens, except *Pseudomonas aeruginosa*. Compound showed good stability to β-lactamases and dehydropeptidase (DHP-I). In systemic infection models in mice, it exhibited excellent activity against *Escherichia coli* O78, *Enterobacter cloacae* M501, *Streptococcus pyogenes* A77 and *Staphylococcus aureus* Y-80-1953, giving ED₅₀ (mg/kg s.c.) values of 1.0, 1.4, 1.2 and 0.9 mg/kg s.c., respectively. Compound is well tolerated and exhibits a good safety profile after both s.c. and i.v. administration. **KR-21056** is an ester-type prodrug with good oral activity.



KR-21056** [253567]: C20 H31 N O8

SOURCE – Korea Res. Inst. Chem. Technol., Taejon (KR).

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3. Kim, J.H. et al. KR-21012, a new carbapenem: I. Synthesis and structure-activity relationships of β-methyl-2-(α-functionalized) carbapenems. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-46.

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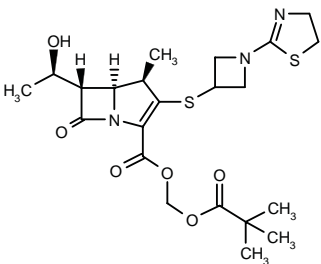
*Identified compound **253564** (see **253031**) Drug Data Report 1997, 019(09): 0818.

Identified compound **253567 (see **253031**) Drug Data Report 1997, 019(09): 0818.

L-084^{3,5,10-17}

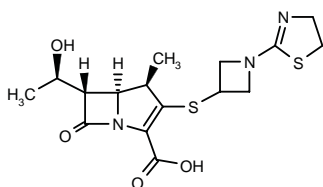
268263

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1-(2-thiazolin-2-yl)azetidin-3-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid pivaloyloxymethyl ester



C22 H31 N3 O6 S2; Mol wt: 497.6339

ACTION – Oral carbapenem prodrug of **LJC-11036** selected for further evaluation based on the excellent antimicrobial activity and high oral absorption. *In vitro*, LJC-11036 shows well-balanced activity against Gram-positive and Gram-negative pathogens, except *Pseudomonas aeruginosa*, with good activity against bacteria isolated from both the respiratory tract (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Moraxella catarrhalis*) and the urinary tract (*Escherichia coli*) including β -lactamase-producing strains, methicillin- and penicillin-resistant strains. In murine respiratory tract infections caused by penicillin-resistant *S. pneumoniae* and *H. influenzae*, L-084 exhibited excellent activity, due in part to good distribution into lung tissue.



LJC-11036^{*,1-17} [**219840**]: C₁₆ H₂₁ N₃ O₄ S₂

SOURCE – Lederle (Japan).

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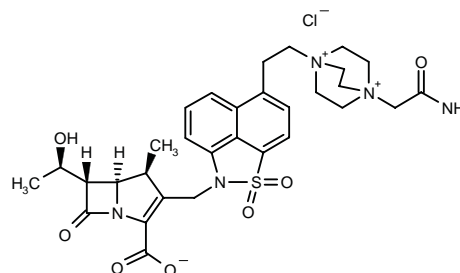
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*Identified compound **219840** Drug Data Report 1995, 017(06): 0551.

L-786392*

258849

(1*S*,5*R*,6*S*)-2-[6-[2-[4-(Carbamoylmethyl)-1,4-diazoniabicyclo[2.2.2]octan-1-yl]ethyl]-1,1-dioxo-2-*H*-naphtho[1,8-*cd*]isothiazol-2-ylmethyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penam-3-carboxylate chloride inner salt



C₃₁ H₃₈ Cl N₅ O₇ S; Mol wt: 660.1882

ACTION – Parenteral carbapenem antibiotic with excellent activity against Gram-positive bacteria including multiply resistant staphylococci, enterococci and pneumococci. *In vivo*, compound exhibited strong activity in several murine infection models including pulmonary infections caused by penicillin-resistant *Streptococcus pneumoniae* or vancomycin-resistant *Enterococcus faecium*, and septicemia caused by *Staphylococcus aureus* or penicillin-resistant *S. pneumoniae*. Compound is well tolerated in several animal species.

SOURCE – Merck & Co.

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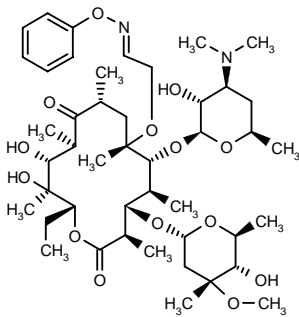
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MISCELLANEOUS ANTIBIOTICS

A-181978

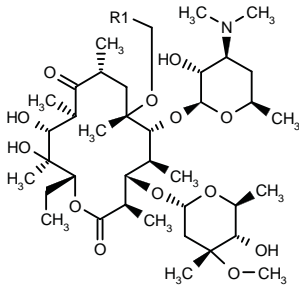
268295

6-Deoxy-6-[2-(phenoxyimino)ethoxy]erythromycin A



C45 H74 N2 O14; Mol wt: 867.0796

ACTION – Macrolide antibiotic with a spectrum of *in vitro* activity and potency comparable to clarithromycin but improved activity against erythromycin-sensitive organisms. It gave MIC values of 0.1, 0.015 and 0.015 µg/ml, respectively, against erythromycin-susceptible *Staphylococcus aureus* 6538P, *Streptococcus pyogenes* EES61 and *Streptococcus pneumoniae* A6303. Other compounds from this series of 6-*O*-substituted erythromycin A derivatives include the following:



Compound	R1	Formula
A-174982* [258950]	ethynyl	C ₄₀ H ₆₉ NO ₁₃
A-177928 [268296]	CN	C ₃₉ H ₆₈ N ₂ O ₁₃
A-181785 [268297]	CH ₂ NHCH ₂ CH ₂ Ph	C ₄₇ H ₈₀ N ₂ O ₁₃

SOURCE – Abbott.

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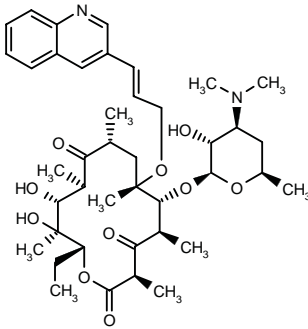
2. Clark, R.F. et al. *Novel 6-O-substituted erythromycin A derivatives. Synthesis and antibacterial activity*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-125.

*Identified compound **258950** (see **257810**) Drug Data Report 1998, 020(02): 0148.

A-184656

268294

6-Deoxy-6-[3-(3-quinoliny)-2(*E*)-propenyloxy]-erythromycin A



C41 H60 N2 O10; Mol wt: 740.9290

ACTION – Antibacterial agent from a series of 6-*O*-substituted ketolides with excellent activity against erythromycin-susceptible Gram-positive bacteria such as *Staphylococcus aureus* 6538P (MIC = 0.2 µg/ml), *Streptococcus pyogenes* EES61 (MIC = 0.2 µg/ml) and *Streptococcus pneumoniae* ATCC 6303 (MIC = 0.03 µg/ml), *S. aureus* A5177 with inducible MLS (macrolide–lincosamide–streptogramin B) resistance (MIC = 0.2 µg/ml) and strains such as *S. pneumoniae* 5949 (MIC = 0.25 µg/ml) and *S. pyogenes* PIU2584 (MIC = 0.1 µg/ml) resistant to erythromycin through an efflux mechanism.

SOURCE – Abbott.

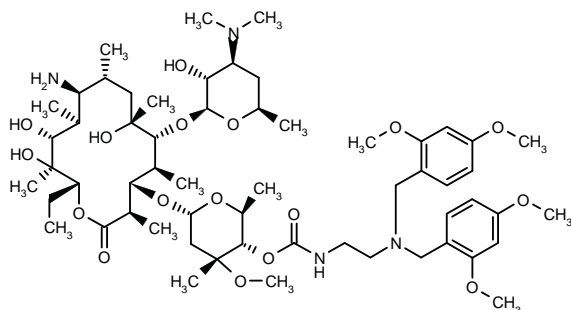
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CP-279107

268264

9-Amino-9-deoxy-4''-O-[N-[2-[N-bis(2,4-dimethoxybenzyl)amino]ethyl]carbamoyl]erythromycin A



C58 H96 N4 O17; Mol wt: 1121.4070

ACTION – Macrolide antibiotic with good activity against erythromycin-resistant *Streptococcus* spp. ($MIC_{90} = 0.06-0.5 \mu\text{g/ml}$); it also shows interesting activity against MLS_B (macrolide-lincosamide-streptogramin B)-resistant strains of *Streptococcus pneumoniae* ($MIC_{50} = 0.03 \mu\text{g/ml}$) and other streptococci ($MIC_{50} = 0.25 \mu\text{g/ml}$). *In vivo*, it was equieffective against infections caused by macrolide-susceptible or -resistant *S. pneumoniae* strains in mice, giving PD_{50} values of 0.5-1.7 mg/kg s.c., although it showed poor oral activity. Compound appears to act by inhibiting protein synthesis on the MLS_B ribosome.

SOURCE – Pfizer.

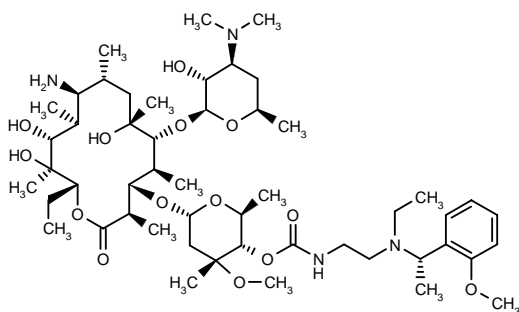
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CP-544372

268265

9-Amino-9-deoxy-4''-O-[N-[2-[N-ethyl-N-[1(S)-(2-methoxyphenyl)ethyl]amino]ethyl]carbamoyl]erythromycin A



C51 H90 N4 O14; Mol wt: 983.2860

ACTION – Macrolide antibiotic equally potent against both macrolide-sensitive (MacS) and -resistant (MacR) strains of *Streptococcus pneumoniae in vitro* ($MIC = 0.06-0.16 \mu\text{g/ml}$) and *in vivo* in mice ($PD_{50} = 5.1$ and $6.6-7.2 \text{ mg/kg p.o.}$, respectively). The agent was also effective against MacS and MacR strains of *Haemophilus influenzae* in mice. Efficacy in animal models of infection correlated more closely with tissue concentrations than with serum levels and results from pharmacokinetic studies in animals indicated the feasibility of once-daily dosing.

SOURCE – Pfizer.

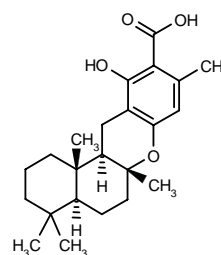
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HONGOQUERCIN A

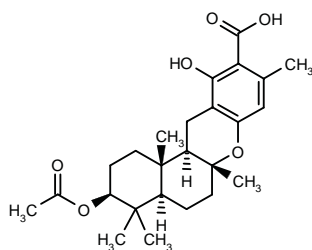
268609

(4a*S*,6a*R*,12a*R*,12b*S*)-11-Hydroxy-4,4,6a,9,12b-pentamethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid



C23 H32 O4; Mol wt: 372.5018

ACTION – Antibacterial agent isolated from the fungus LL-23G227, with moderate activity against Gram-positive bacteria such as *Staphylococcus aureus* 310, *Enterococcus faecalis* and *Enterococcus faecium* ($MIC = 2 \mu\text{g/ml}$), but inactive against Gram-negative strains and *Candida albicans*. Compound was active against *Escherichia coli imp* ($MIC = 4 \mu\text{g/ml}$) but not against wild-type *E. coli* strains, suggesting that it does not penetrate the normal Gram-negative outer cell membrane well. Its antibacterial activity appears to be related to bacterial membrane damage. Another compound isolated from this source is:



Hongoquercin B [268610]: C₂₅ H₃₄ O₆

SOURCE – Wyeth-Ayerst.

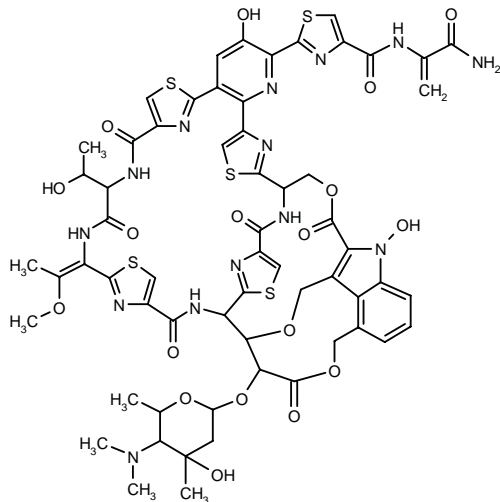
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MJ-347-81F4 A

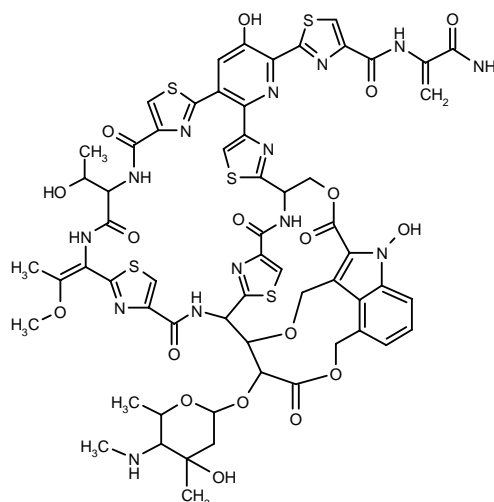
268611

2-[4-[N-(1-Carbamoylviny)l)carbamoyl]thiazol-2-yl]-49-[5-(dimethylamino)-4-hydroxy-4,6-dimethyltetrahydropyran-2-yloxy]-3,29-dihydroxy-11-(1-hydroxyethyl)-14-(1-methoxyethylidene)-9,10,11,12,13,14,19,20,21,22,29,30,32,33-tetradecahydro-24H-22,25-(ethanoxymethano)-8,5:18,15:37,34-trinitrilo-21,33-([2,4]-endo-thiazolo-methanimino)pyrido[3',2':20,21][1,28,8,18,24,4,11,14]-dioxatrithiotriazacyclodotriacontino[30,31-b]indole-9,12,19,30,40,48-hexaone



C₆₁ H₆₀ N₁₄ O₁₈ S₅; Mol wt: 1437.5550

ACTION – The major component of an antibiotic complex produced by *Amycolatopsis* sp. MJ347-81F4, with excellent *in vitro* activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis* (MIC = 0.006-0.2 µg/ml). Compound was not active against Gram-negative bacteria but showed an antifungal spectrum including *Candida* spp. and *Saccharomyces cerevisiae*. It appears to act by inactivating the 50S subunit of the ribosome, resulting in inhibition of protein synthesis. Another component of this antibiotic complex is:



MJ-347-81F4 B [268612]: C₆₀ H₅₈ N₁₄ O₁₈ S₅

SOURCE – Taiho.

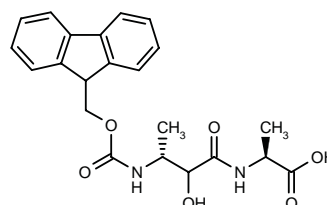
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VRC-374

268307

N-[3(*R*)-[(9*H*-Fluoren-9-ylmethoxy)carboxamido]-2-hydroxybutyramido]-L-alanine



C₂₂ H₂₄ N₂ O₆; Mol wt: 412.4396

ACTION – Antibiotic that inhibits Mur ligases, enzymes involved in bacterial peptidoglycan synthesis.

SOURCE – Versicor.

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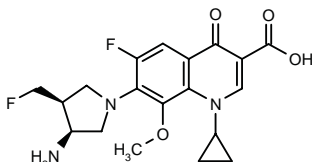
1. Chen, D. et al. *Pathway screening: Novel technology for identifying inhibitors of MurA-F in a single incubation.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-160.
2. Rosenow, C. and Trias, J. *Mur ligases in S. pneumoniae targets for novel antibiotic development.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-165.

MISCELLANEOUS ANTIBACTERIAL DRUGS

DC-756

268240

(3*S*,4*S*)-7-[3-Amino-4-(fluoromethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C19 H21 F2 N3 O4; Mol wt: 393.3879

ACTION – Antibacterial agent from a series of 8-methoxyquinolones with broad-spectrum activity against Gram-positive and Gram-negative bacteria including quinolone-resistant strains. Its activity was superior to that of other quinolones (levofloxacin, ciprofloxacin, sparfloxacin) against Gram-positive bacteria such as ofloxacin/methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae* and *Enterococcus faecalis* (MIC = 0.39-0.78, 0.025, 0.025 and 0.1 µg/ml, respectively); good activity was observed against a range of aerobic and anaerobic bacteria. Furthermore, the compound showed favorable physico-chemical properties, a good pharmacokinetic profile and low toxicity in animals.

SOURCE – Daiichi Pharmaceutical.

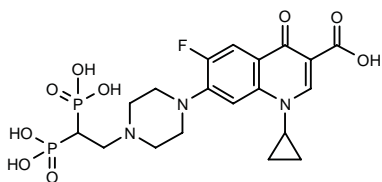
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3. Tanaka, M. et al. *DC-756: A new methoxyquinolone: In vitro antibacterial activity against clinical isolates.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-74.
4. Yabe, K. et al. *DC-756: A new methoxyquinolone: Toxicological and pharmacokinetic evaluation.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-72.

ENC-41-HP

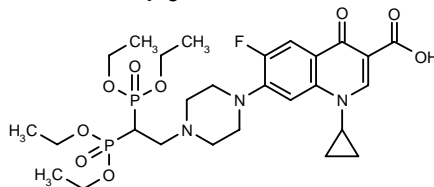
268301

1-Cyclopropyl-7-[4-(2,2-diphosphonoethyl)piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C19 H24 F N3 O9 P2; Mol wt: 519.3566

ACTION – Fluoroquinolone conjugated to a bisphosphonate that binds to bone, with potential in the treatment of bone and connective tissue infections. In contrast to the fluoroquinolone moiety ciprofloxacin, ENC-41-HP was able to inhibit the growth of *Staphylococcus aureus* bound to bone, and it also inhibited the growth of Gram-negative bacteria. Another conjugate is:



ENC-22-HP [268300]: C27 H40 F N3 O9 P2

SOURCE – ElizaNor Biopharmaceuticals.

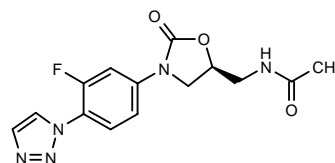
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PNU-140457*

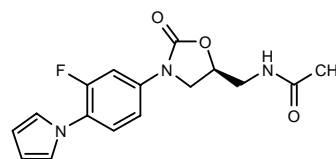
242221

N-[3-[3-Fluoro-4-(1,2,3-triazol-1-yl)phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C14 H14 F N5 O3; Mol wt: 319.2946

ACTION – Oxazolidinone antibacterial agent active against Gram-positive pathogens including *Staphylococcus aureus* and *Streptococcus pneumoniae* (MIC < 0.5-1 µg/ml) and against Gram-negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC = 2-4 µg/ml). Compound is about 2-4 times more active than linezolid. It gave an ED₅₀ of 4.7 mg/kg p.o. in mice with infections caused by *S. aureus* 9213 (ED₅₀ vancomycin = 2.0 mg/kg). Another compound from this series of azolyphenyloxazolidinones with a similar *in vitro* profile but poor *in vivo* activity is:



PNU-107922 [268128]: C16 H16 F N3 O3

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Hutchinson, D.K. (Pharmacia & Upjohn AB) *Hetero-aromatic ring subst. phenyloxazolidinone antimicrobials*. EP 807112, JP 98513446, WO 9623788.

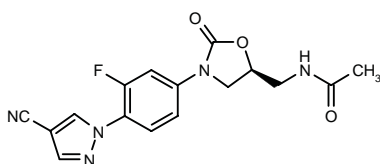
2. Hutchinson, D.K. et al. *Synthesis and antibacterial activity of azolyphenyl-oxazolidinones having nitrogen-bound five-membered heterocyclic rings*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-137.

*Identified compound **242221** (see **240938**) Drug Data Report 1996, 018(11): 1004.

PNU-172576

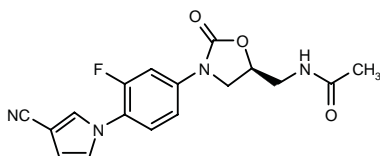
268126

N-[3-[4-(4-Cyano-1*H*-pyrazol-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5(*S*)-ylmethyl]acetamide



C16 H14 F N5 O3; Mol wt: 343.3166

ACTION – Oxazolidinone antibacterial agent with potent activity against Gram-positive and Gram-negative organisms such as methicillin-susceptible and -resistant *Staphylococcus aureus* (MIC = 0.5 µg/ml), *Streptococcus pneumoniae* (MIC < 0.125 µg/ml), *Enterococcus faecalis* (MIC = 0.5 µg/ml), *Haemophilus influenzae* (MIC = 4 µg/ml) and *Moraxella catarrhalis* (MIC = 2 µg/ml). *In vivo*, it was about 3 times more active than eperezolid or linezolid in mice with lethal systemic infections caused by *S. aureus* (ED₅₀ = 1.2 mg/kg p.o. vs. 3.3 mg/kg for eperezolid) and *S. pneumoniae* (ED₅₀ < 0.6 mg/kg p.o. vs. 1.8 mg/kg for linezolid). Compound shows very good oral bioavailability (80%) in rats. Another azolyphenyl oxazolidinone with a similar profile is:



PNU-171933 [268266]: C17 H15 F N4 O3

SOURCE – Pharmacia & Upjohn.

REFERENCES

1. Hutchinson, D.K. (Pharmacia & Upjohn AB) *Hetero-aromatic ring subst. phenyloxazolidinone antimicrobials*. EP 807112, JP 98513446, WO 9623788.

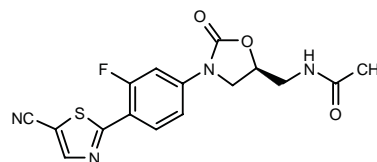
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3. Genin, M.J. et al. *Substituent effects on the antibacterial activity of novel highly potent nitrogen-bound azolyphenyl oxazolidinones*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-138.

PNU-176798

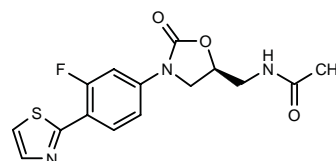
268267

N-[3-[4-(5-Cyano-1,3-thiazol-2-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5(*S*)-ylmethyl]acetamide



C16 H13 F N4 O3 S; Mol wt: 360.3677

ACTION – Oxazolidinone antibacterial agent with potent activity against Gram-positive and Gram-negative strains including methicillin-susceptible and -resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC < 0.125 µg/ml against Gram-positive strains; MIC = 2 and 0.5 µg/ml, respectively, against *H. influenzae* and *M. catarrhalis*), being significantly more active than linezolid. *In vivo*, it showed excellent activity against murine *S. aureus* SA9213 infections (ED₅₀ = 1.1 mg/kg). Another related compound is:



PNU-174069 [268127]: C15 H14 F N3 O3 S

SOURCE – Pharmacia & Upjohn.

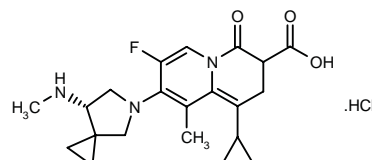
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A-170568.1

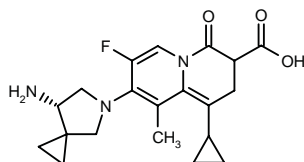
268134

1-Cyclopropyl-7-fluoro-9-methyl-8-[7(*S*)-(methylamino)-5-azaspiro[2.4]hept-5-yl]-4-oxo-3,4-dihydro-2*H*-quinolizine-3-carboxylic acid hydrochloride



C21 H26 F N3 O3 . HCl; Mol wt: 423.9133

ACTION – Orally active 2-pyridone antibacterial agent, a potent DNA gyrase inhibitor with excellent and broad-spectrum activity against aerobic and anaerobic pathogens including ciprofloxacin- and vancomycin-resistant strains. It was active *in vivo* in rats infected with resistant Gram-positive strains such as vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*, and penicillin-resistant *Streptococcus pneumoniae*, whereas vancomycin and ciprofloxacin were ineffective. Compound is also relatively nontoxic. It is under consideration for clinical development. Another 2-pyridone antibiotic with potent, broad-spectrum activity is:



A-165753 [268133]: C₂₀ H₂₄ F N₃ O₃

SOURCE – Abbott.

REFERENCES

1. Armiger, Y.L. et al. *The discovery of A-165753 and A-170568, two potent broad-spectrum antimicrobial agents*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-86.
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PARASIN I

268130

Lysyl-glycyl-arginyl-glycyl-lysyl-glutaminy-glycyl-glycyl-lysyl-valyl-arginyl-alanyl-lysyl-alanyl-lysyl-threonyl-arginyl-seryl-serine

C₈₂ H₁₅₄ N₃₄ O₂₄; Mol wt: 2000.3330

ACTION – Antimicrobial peptide produced by the catfish *Parasilurus asotus* in response to epidermal injury. The peptide showed potent and broad-spectrum antimicrobial activity, being at least 12 times more potent than magainin 2, and was devoid of hemolytic activity.

SOURCE – Korea Adv. Inst. Sci. Technol., Taejon (KR).

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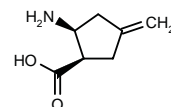
ANTIFUNGAL AGENTS

BAY-10-8888

268135

207201 (as *cis*-isomer)*

(-)-(1*R*,2*S*)-2-Amino-4-methylenecyclopentane-1-carboxylic acid



C₇ H₁₁ N O₂; Mol wt: 141.1689

ACTION – Antifungal agent with potent anti-*Candida* activity that actively accumulates in cells and inhibits isoleucyl-tRNA synthetase (isoleucine-tRNA ligase), blocking protein biosynthesis and cell growth.

SOURCE – Bayer.

REFERENCES

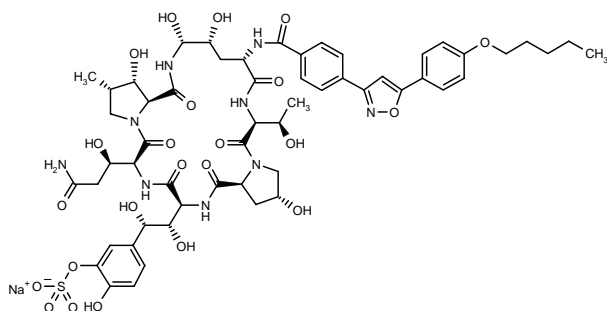
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2. Mittendorf, J. (Bayer AG) *Efficient and highly enantioselective process for the preparation of enantiomerically pure cyclopentane-β-amino acids*. EP 805145.
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4. Ziegelbauer, K. *Decreased accumulation or increased isoleucyl-tRNA synthetase activity confers resistance to the cyclic β-amino acid BAY 10-8888 in Candida albicans and Candida tropicalis*. Antimicrob Agents Chemother 1998, 42(7): 1581.
5. Ziegelbauer, K. et al. *Molecular mode of action of the antifungal β-amino acid BAY 10-8888*. Antimicrob Agents Chemother 1998, 42(9): 2197.

*See **203878** Drug Data Report 1994, 016(05): 0486.

FK-463

263634

(3*S*,6*S*,9*S*,11*R*,15*S*,18*S*,20*R*,21*R*,24*S*,25*R*,26*S*)-3-[3-Amino-1(*R*)-hydroxy-3-oxopropyl]-6-[1(*S*),2(*S*)-dihydroxy-2-(4-hydroxy-3-sulfooxyphenyl)ethyl]-11,20,21,25-tetrahydroxy-15-[1(*R*)-hydroxyethyl]-26-methyl-18-[4-[5-[4-(pentyloxy)phenyl]isoxazol-3-yl]benzamido]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.0^{9,13}]heptacosane-2,5,8,14,17,23-hexaone sodium salt



C56 H70 N9 Na O23 S; Mol wt: 1292.2650

ACTION – A water-soluble echinocandin-like lipopeptide antifungal agent for parenteral administration that acts by inhibiting 1,3-β-D-glucan synthase. Broad-spectrum antifungal activity was demonstrated, with MICs against clinical isolates of *Candida* spp. of < 0.0039-2 μg/ml and of < 0.0039-0.0313 μg/ml against *Aspergillus* spp.; it was active against azole-resistant *Candida albicans*. FK-463 was fungicidal against *Candida* and fungistatic against *Aspergillus fumigatus*. It exhibited comparable activity to amphotericin B *in vivo* in murine models of disseminated candidiasis (ED₅₀ = 0.21-1.00 mg/kg/day i.v.) and aspergillosis (ED₅₀ = 0.25-0.50 mg/kg/day i.v.). Results from a phase I study in healthy males showed the agent to be safe when administered as single doses (2.5-50 mg by 2-h infusion) and multiple doses (25 mg/day for 7 days).

SOURCE – Fujisawa.

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- Suzuki, S. et al. *Pharmacokinetics of FK463, a novel water-soluble echinocandin-like lipopeptide, in animals*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-144.
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8. Wakai, Y. et al. *Efficacy of FK463, a novel water-soluble echinocandin-like lipopeptide, in murine models of pulmonary aspergillosis*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-143.

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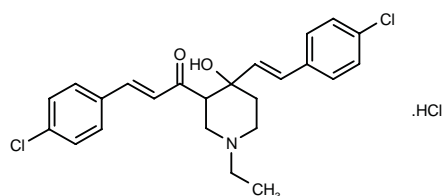
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MONOGRAPH – Fromtling, R.A. and Castañer, J. *FK-463*. Drugs Fut 1998, 023(12): 1273.

NC-1175

241097

3-(4-Chlorophenyl)-1-[4-[2(*E*)-(4-chlorophenyl)vinyl]-1-ethyl-4-hydroxy-3-piperidinyl]-2(*E*)-propen-1-one hydrochloride



C24 H25 Cl2 N O2 . HCl; Mol wt: 466.8334

ACTION – Lipophilic α,β-unsaturated styryl ketone with activity against a broad spectrum of pathogenic fungi including azole- and polyene-resistant *Candida* and *Aspergillus*. Exposure of fungal cells to the compound at MIC (3.12-12.5 μM) and super MIC concentrations induced > 99.9% cell killing within 8 h. It inhibited H⁺-ATPase of *Candida* and *Aspergillus* in a concentration-dependent manner at 3.12-25 μM, resulting in sudden intracellular acidification and cell death, suggesting that this enzyme is the primary target of action.

SOURCES – University of Saskatchewan, Saskatoon, SK (CA); Wayne State University, Detroit, MI (US).

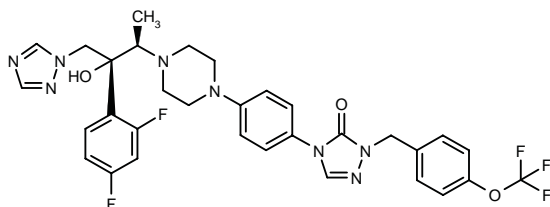
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- Vashishtha, S.C. et al. *Antifungal activity of some quaternary ammonium salts of 4-(2-arylvinyl)-3-(3-aryl-2-propenoyl)-1-ethyl-4-piperidinols and related compounds*. Pharmazie 1998, 53(7): 499.

SYN-2869

268123

4-[4-[4-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1-piperazinyl]phenyl]-2-[4-(trifluoromethoxy)benzyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one



C32 H31 F5 N8 O3; Mol wt: 670.6399

ACTION – Orally active triazole antifungal agent with broad-spectrum and potent activity against a variety of pathogenic fungi both *in vitro* and *in vivo*. *In vitro*, it was active against pathogenic yeasts such as *Candida* spp. and *Cryptococcus neoformans*, filamentous fungi such as *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger*, as well as molds. *In vivo*, the selective distribution of SYN-2869 into lung tissue appeared to contribute to its excellent activity in several murine fungal infections caused by *Candida albicans*, *Candida glabrata*, *C. neoformans* and *A. fumigatus*.

SOURCES – Synphar; Taiho.

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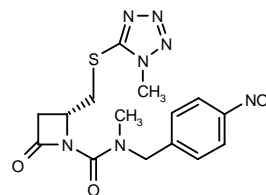
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ANTIVIRAL DRUGS

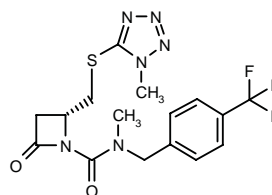
269051

N-Methyl-2(*R*)-(1-methyl-1*H*-tetrazol-5-ylsulfanylmethyl)-(4-nitrobenzyl)-4-oxoazetidine-1-carboxamide



C15 H17 N7 O4 S; Mol wt: 391.4103

ACTION – Monobactam inhibitor of human cytomegalovirus (HCMV) protease (IC₅₀ = 0.8 μM) with selectivity relative to human leukocyte elastase (HLE; IC₅₀ = 69 μM), shown to have antiviral activity against HCMV in a plaque reduction assay (EC₅₀ = 78 μM); it is also reported to penetrate into cells and inhibit HCMV protease. Another compound with a similar profile of activity is:

**269050:** C16 H17 F3 N6 O2 S

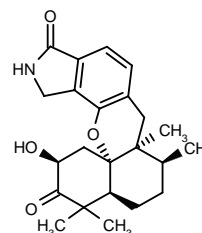
SOURCE – Boehringer Ingelheim.

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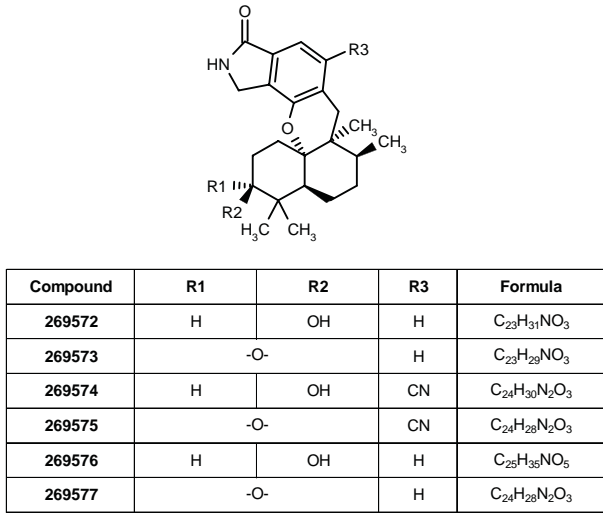
269571

(6*aS*,7*S*,9*aR*,12*S*,13*aS*)-12-Hydroxy-6*a*,7,10,10-tetramethyl-2,3,6,6*a*,7,8,9,9*a*,10,11,12,13-dodecahydro-1*H*-naphtho[1',8':5,6]pyrano[2,3-*e*]isoindole-3,11-dione



C23 H29 N O4; Mol wt: 383.4851

ACTION – Antiviral agent active against influenza A virus, with low cytotoxicity in uninfected cells. Other compounds from this series of sesquiterpene derivatives include the following:



SOURCE – Shionogi.

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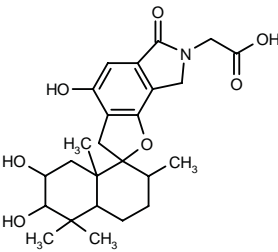
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AIDS MEDICINES

Mer-VGF724C

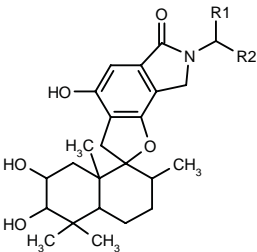
269786

2-(4,6',7'-Trihydroxy-2',5',5',8'a-tetramethyl-6-oxo-3,6,7,8-tetrahydro-2*H*-spiro[furo[2,3-*e*]isoindole-2,1'-octahydro-naphthalen]-7-yl)acetic acid



C₂₅ H₃₃ N O₇; Mol wt: 459.5357

ACTION – Antiviral agent for AIDS isolated from *Stachybotrys* sp. Mer-VGF724 (FERM P-153), with HIV protease-inhibitory activity (41% inhibition at 100 µg/ml). Other compounds isolated from the same source include the following:



Compound	R1	R2	Formula
Mer-VGF724A [269787]	CO ₂ H	CH ₂ CH ₂ CO ₂ H	C ₂₈ H ₃₇ NO ₉
Mer-VGF724B [269788]	CH ₂ CH ₂ CO ₂ H	H	C ₂₇ H ₃₇ NO ₇
Mer-VGF724D [269789]	CO ₂ H	Me	C ₂₆ H ₃₅ NO ₇

SOURCE – Mercian.

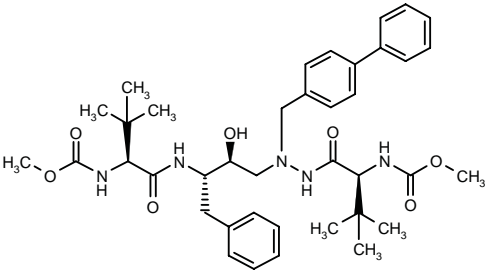
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CGP-75355*2,4

253172

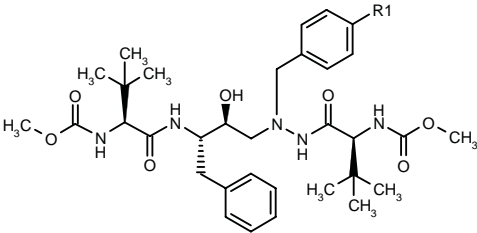
N-(Methoxycarbonyl)-*L*-*tert*-leucine *N*²-(biphenyl-4-yl-methyl)-*N*²-[2(*S*)-hydroxy-3(*S*)-[*N*-(methoxycarbonyl)-*L*-*tert*-leucylamino]-4-phenylbutyl]hydrazide



C₃₉ H₅₃ N₅ O₇; Mol wt: 703.8757

M.p. 210-1 °C, [α]_D –58° (c 1 EtOH).

ACTION – Orally active azadipeptide antiviral agent for AIDS that acts by inhibiting HIV protease (IC₅₀ = 58 nM). It displayed potent antiviral activity in HIV-1/MN-infected MT-2 cells (ED₅₀ = 0.7 nM; ED₉₀ = 3 nM) and was active against drug-resistant strains of HIV (ED₅₀ = 0.01-0.9 µM) including indinavir- and saquinavir-resistant strains. Other related compounds qualifying for further evaluation as potential clinical candidates include the following:



Compound	R1	Formula
CGP-75176** [258682] ^{1,3,4}	2-Me-5-tetrazolyl	C ₃₅ H ₅₁ N ₉ O ₇
CGP-75136 [268102] ^{1,3,4}	2-thiazolyl	C ₃₆ H ₅₀ N ₆ O ₇ S

SOURCE – Novartis.

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*Identified compound **253172** (see **252410**) Drug Data Report 1997, 019(09): 0826.

Identified compound **258682 (see **257722**) Drug Data Report 1998, 020(02): 0155.

EFAVIRENZ

207217

(S)-(-)-6-Chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1H-3,1-benzoxazin-2-one

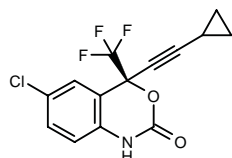
DMP-266

L-741211 (racemic)

L-743725 [as (+)-isomer]

L-743726⁺

StocrinTM



C14 H9 Cl F3 N O2; Mol wt: 315.6771

ACTION – Non-nucleoside HIV-1 reverse transcriptase inhibitor.

INDICATION – Treatment of HIV-1 infection in combination with other antiretroviral agents.

PRESENTATION – Capsules, 50, 100 and 200 mg.

PROPRIETARY NAME – Sustiva (US).

SOURCE – DuPont Pharmaceuticals.

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*Drug Data Report 1994, 016(06): 0581.

FOMIVIRSEN SODIUM

196030

2'-Deoxy-P-thioguananylyl-(5'→3')-2'-deoxy-P-thiocytidylyl-(5'→3')-2'-deoxy-P-thioguananylyl-(5'→3')-P-thiothymidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-2'-deoxy-P-thioguananylyl-(5'→3')-2'-deoxy-P-thiocytidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-2'-deoxy-P-thiocytidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-2'-deoxy-P-thiocytidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-2'-deoxy-P-thiocytidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-P-thiothymidylyl-(5'→3')-2'-deoxy-P-thioguananylyl-(5'→3')-2'-deoxy-P-thiocytidylyl-(5'→3')-2'-deoxyguanosine eicosasodium salt

d(P-thio)(G-C-G-T-T-T-T-G-C-T-C-T-T-C-T-T-C-T-T-G-C-G)deoxyribonucleic acid eicosasodium salt

ISIS-2922⁺

C204 H243 N63 Na20 O114 P20 S20; Mol wt: 7122.16

ACTION – Antisense phosphorothioate oligonucleotide that inhibits human cytomegalovirus (HCMV) replication. The nucleotide sequence is complementary to a sequence in mRNA transcripts of the major immediate early region 2 (IE2) of HCMV, a region encoding several proteins responsible for the regulation of viral gene expression that are essential for the production of infectious CMV; binding of fomivirsen to the target mRNA inhibits IE2 protein synthesis, resulting in inhibition of virus replication.

INDICATION – Local treatment of CMV retinitis in patients with AIDS who are intolerant of or have a contraindication to other treatments for CMV retinitis, or who were insufficiently responsive to previous treatments.

PROPRIETARY NAME – *Vitravene* (US).

SOURCES – Ciba Vision; Isis Pharmaceuticals.

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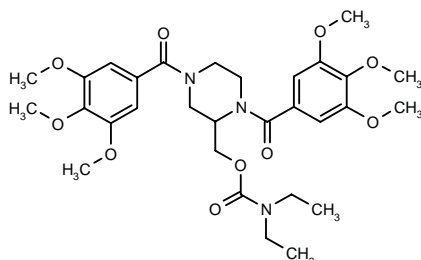
*Drug Data Report 1994, 016(06): 0576.

MFH-1

268302

N,N-Diethylcarbamic acid 1,4-bis(3,4,5-trimethoxybenzo-yl)piperazin-2-ylmethyl ester

PMS-601



C30 H41 N3 O10; Mol wt: 603.6649

ACTION – PAF antagonist with potential as an adjunct in the treatment of AIDS. In HIV-1-infected monocyte-derived macrophages, it inhibited retroviral replication with ED₅₀ values of 7-18 µM, in the absence of cytotoxicity; compound interacted with an early phase of the HIV life cycle. Its antiviral effects were associated with decreases in PAF secretion (20% at 100 µM), as well as RANTES and MIP-1α synthesis (37 and 52%, respectively, at 100 µM), but it had no effect on TNF-α, IL-6 or MIP-1β production. It was also shown to potentiate the antiviral activity of zidovudine (AZT).

SOURCE – Université Paris 7 Denis Diderot, Paris (FR).

REFERENCES

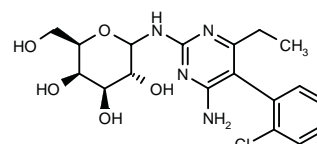
1. Heymans, F. et al. *Design and modeling of new PAF antagonists: 1,4-Bis-(3',4',5'-trimethoxybenzoyl)-2-substituted carbonyloxymethylpiperazines.* J Lipid Mediators Cell Signal 1994, 10(1-2): 153.

2. Martin, M. et al. *Anti-HIV activity, mode of action, and effects on AZT activity of MFH-1, a PAF antagonist.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-22.

TREATMENT OF PROTOZOAL DISEASES

268973

5-(2-Chlorophenyl)-6-ethyl-2-(D-galactopyranosylamino)-pyrimidine-4-amine



C18 H23 Cl N4 O5; Mol wt: 410.8557

ACTION – Galactosyl conjugate of the known antimalarial agent pyrimethamine designed for site-specific delivery to the liver, where it is degraded by hydrolases to the parent drug, thus allowing high concentrations of the drug to be achieved in the liver to act against the liver stage of the malaria parasite, contrary to pyrimethamine, which is only active *in vivo* against the erythrocyte stage of the parasite. *In vitro*, compound was shown to produce 84% inhibition of the number of schizonts in *Plasmodium yoelii* sporozoite-overlaid murine hepatocytes at a concentration of 50 µM, compared to 32% inhibition for pyrimethamine at the same concentration.

SOURCE – Oxford GlycoSciences.

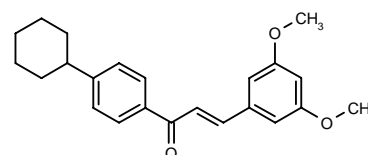
REFERENCES

1. Courtney, S.M. et al. (Oxford GlycoSciences Ltd.) *Therapeutic cpds.* WO 9828318.

PH-104¹⁻³

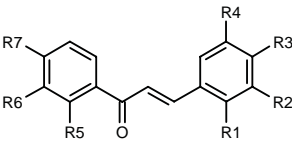
268290

1-(4-Cyclohexylphenyl)-3-(3,5-dimethoxyphenyl)-2(*E*)-propen-1-one



C23 H26 O3; Mol wt: 350.4554

ACTION – Antimicrobial agent, a chalcone derivative with antileishmanial activity proven to inhibit the growth of *Leishmania donovani* amastigotes and *Leishmania major* promastigotes in a concentration-dependent fashion, and to prevent lesion development in mice infected with *L. major* when applied topically at a concentration of 50 mg/g b.i.d. for 10 days. The compound also displayed antibacterial activity against *Helicobacter pylori* (MIC = 8-32 µg/ml). Other related chalcones are:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
PH-81 [268403] ^{1,2}	OH	H	OH	H	H	OBu	H	C ₁₉ H ₂₀ O ₄
PH-74 [268404] ²	F	H	F	H	H	H	OMe	C ₁₆ H ₁₂ F ₂ O ₂
PH-98 [268405] ^{2,3}	NO ₂	H	H	H	OMe	OMe	OMe	C ₁₈ H ₁₇ NO ₆
PH-135 [268406] ²	H	OMe	H	OMe	F	H	H	C ₁₇ H ₁₅ FO ₃
PH-136 [268407] ²	H	OMe	H	OMe	H	F	H	C ₁₇ H ₁₅ FO ₃

SOURCES – Royal Danish School of Pharmacy, Copenhagen (DK); Statens Serum Institute, Copenhagen (DK).

REFERENCES

1. Chen, M. et al. *Antileishmanial activity of novel chalcones*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-193.

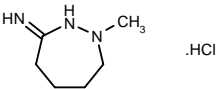
2. Kharazmi, A. et al. *Inhibition of in vitro growth of Helicobacter pylori, Legionella pneumophila, and some Gram-positive bacteria by chalcones*. 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst F-192.

3. Nielsen, S.F. et al. *Antileishmanial chalcones: Statistical design, synthesis, and three-dimensional quantitative structure-activity relationship analysis*. J Med Chem 1998, 41(24): 4819.

TREATMENT OF SEPTIC SHOCK

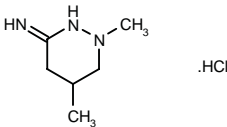
267826

1-Methylperhydro-1,2-diazepin-3-imine hydrochloride

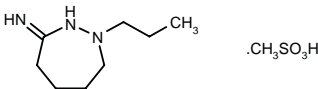


C₆ H₁₃ N₃ . HCl; Mol wt: 163.6506

ACTION – Agent for the treatment or prevention of shock, hypotension, rheumatoid arthritis, ulcerative colitis, cerebral ischemia, cancer and insulin-dependent diabetes, an inhibitor of inducible nitric oxide synthase (iNOS; IC₅₀ = 0.02 μM in lipopolysaccharide [LPS]-treated murine macrophage cells). Other related compounds include the following:



267827: C₆ H₁₃ N₃ . HCl



267828: C₈ H₁₇ N₃ . C H₄ O₃ S

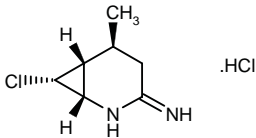
SOURCE – Ono.

REFERENCES

1. Taniguchi, N. et al. (Ono Pharmaceutical Co., Ltd.) *NOS inhibitors*. JP 98182618.

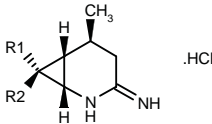
269542

(+)-(1α,5α,6α,7β)-7-Chloro-5-methyl-2-azabicyclo-[4.1.0]heptan-3-imine hydrochloride

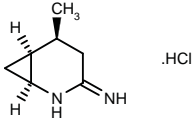


C₇ H₁₁ Cl N₂ . HCl; Mol wt: 195.0918

ACTION – An inhibitor of inducible nitric oxide synthase (iNOS; IC₅₀ = 0.012 μM) with potential in the treatment or prevention of septic shock, heart failure, multiple organ failure, tuberculosis, rheumatoid arthritis, hypotension, ulcerative colitis, autoimmune diseases, cerebral ischemia, disseminated intravascular coagulation (DIC), arteriosclerosis, insulin-dependent diabetes, cancer and Alzheimer's disease. Within this series of condensed piperidine derivatives, the following are also included:



Compound	R1	R2	Isomer	Formula
269543	Me	H	racemic	C ₈ H ₁₄ N ₂ .HCl
269544	H	H	racemic	C ₇ H ₁₂ N ₂ .HCl
269545	Cl	H	racemic	C ₇ H ₁₁ ClN ₂ .HCl
269547	Cl	Cl	(+)-isomer	C ₇ H ₁₀ Cl ₂ N ₂ .HCl
269548	Cl	Cl	racemic	C ₇ H ₁₀ Cl ₂ N ₂ .HCl



269546: C₇ H₁₂ N₂ . HCl

SOURCE – Ono.

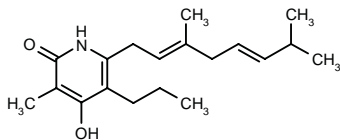
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1. Taniguchi, N. et al. (Ono Pharmaceutical Co., Ltd.) *Condensed piperidine derivs. used as a nitrogen monoxide synthase inhibitors*. EP 870763.

NK-26588

269313

6-[3,7-Dimethyl-2(*E*),5(*E*)-octadienyl]-4-hydroxy-3-methyl-5-propylpyridin-2(1*H*)-one



C₁₉ H₂₉ N O₂; Mol wt: 303.4431

ACTION – An inhibitor of nitric oxide synthase (NOS) isolated from *Streptomyces* NA26588 (FERM-P-16005), proven to inhibit the inducible isoform (iNOS) with an IC₅₀ of 2.0 µg/ml in murine macrophages stimulated with endotoxin + interferon gamma. No toxicity was observed in mice at a dose of 100 mg/kg i.p. Potentially useful for the treatment of septic shock, arthritis, stroke, cerebral ischemia, Parkinson's disease and insulin-dependent diabetes.

SOURCE – Nippon Kayaku.

REFERENCES

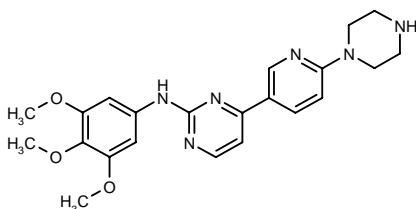
1. Sukenaga, Y. et al. (Nippon Kayaku Co., Ltd.) *Novel bioactive substance NK26588, its preparation method and its use.* JP 98237044.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

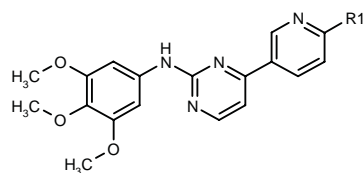
265115

N-[4-[6-(1-Piperazinyl)pyridin-3-yl]pyrimidin-2-yl]-*N*-(3,4,5-trimethoxyphenyl)amine



C₂₂ H₂₆ N₆ O₃; Mol wt: 422.4864

ACTION – Potent and selective inhibitor of the protein tyrosine kinases ZAP-70 and syk with good selectivity over other kinases such as cdc2, epidermal growth factor (EGF) receptor, p56^{lck}, protein kinase C and csk. Potentially useful for the treatment or prevention of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and psoriasis, graft-versus-host disease, transplant rejection, allergic diseases such as asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis, and disorders involving inappropriate platelet activation. Other compounds from this series of 2-pyrimidineamine derivatives include the following:



Compound	R1	Formula
268136	perhydro-1,4-diazepin-1-yl	C ₂₃ H ₂₈ N ₆ O ₃
268137	4-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268138	3-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268139	3(S)-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268140	3(R)-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268141	4-Et-1-Piz	C ₂₄ H ₃₀ N ₆ O ₃
268142	3,5-(Me)2-1-Piz	C ₂₄ H ₃₀ N ₆ O ₃
268143	3-(CH2OH)-1-Piz	C ₂₃ H ₂₈ N ₆ O ₄
268144	3-[N(Me)2CH2]-1-Piz	C ₂₅ H ₃₃ N ₇ O ₃

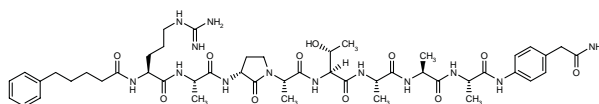
SOURCE – Celltech.

REFERENCES

1. Davis, P.D. et al. (Celltech Therapeutics Ltd.) *2-Pyrimidineamine derivs. and processes for their preparation.* WO 9818782.

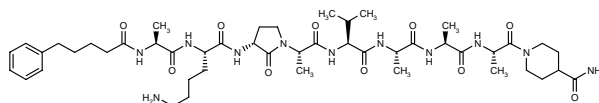
266206

2-[4-[2(*S*)-[3(*R*)-(5-Phenylpentanoyl-arginyl-alanyl)amino]-2-oxopyrrolidin-1-yl]propionyl-threonyl-alanyl-alanyl-alanyl]phenyl]acetamide

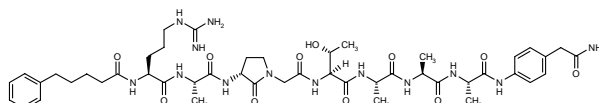


C₄₈ H₇₁ N₁₃ O₁₁; Mol wt: 1006.1690

ACTION – Agent for the treatment of autoimmune diseases and inflammatory disorders such as rheumatoid arthritis and multiple sclerosis, a peptide that binds to major histocompatibility complex (MHC) class II molecules and inhibits T-cell activation by selfantigens characteristic of autoimmune diseases. *In vitro*, compound was found to bind to purified HLA-DR4Dw4 at a concentration of 0.1 µM or much less. *In vivo*, it was active in a delayed-type hypersensitivity model in mice when administered at a dose < 0.1 mg/kg/day using osmotic minipumps. Other specifically claimed peptides include the following:



267207: C₄₇ H₇₅ N₁₁ O₁₀

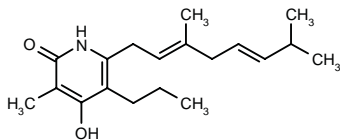


267208: C₄₇ H₆₉ N₁₃ O₁₁

NK-26588

269313

6-[3,7-Dimethyl-2(*E*),5(*E*)-octadienyl]-4-hydroxy-3-methyl-5-propylpyridin-2(1*H*)-one



C₁₉H₂₉N O₂; Mol wt: 303.4431

ACTION – An inhibitor of nitric oxide synthase (NOS) isolated from *Streptomyces* NA26588 (FERM-P-16005), proven to inhibit the inducible isoform (iNOS) with an IC₅₀ of 2.0 µg/ml in murine macrophages stimulated with endotoxin + interferon gamma. No toxicity was observed in mice at a dose of 100 mg/kg i.p. Potentially useful for the treatment of septic shock, arthritis, stroke, cerebral ischemia, Parkinson's disease and insulin-dependent diabetes.

SOURCE – Nippon Kayaku.

REFERENCES

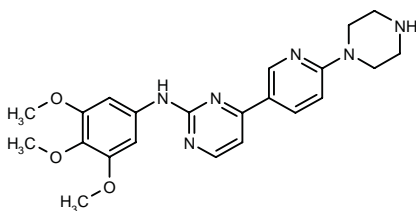
1. Sukenaga, Y. et al. (Nippon Kayaku Co., Ltd.) *Novel bioactive substance NK26588, its preparation method and its use.* JP 98237044.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

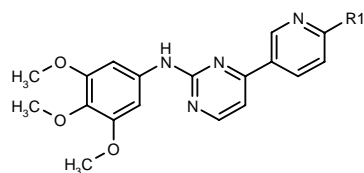
265115

N-[4-[6-(1-Piperazinyl)pyridin-3-yl]pyrimidin-2-yl]-*N*-(3,4,5-trimethoxyphenyl)amine



C₂₂H₂₆N₆O₃; Mol wt: 422.4864

ACTION – Potent and selective inhibitor of the protein tyrosine kinases ZAP-70 and syk with good selectivity over other kinases such as cdc2, epidermal growth factor (EGF) receptor, p56^{lck}, protein kinase C and csk. Potentially useful for the treatment or prevention of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and psoriasis, graft-versus-host disease, transplant rejection, allergic diseases such as asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis, and disorders involving inappropriate platelet activation. Other compounds from this series of 2-pyrimidineamine derivatives include the following:



Compound	R1	Formula
268136	perhydro-1,4-diazepin-1-yl	C ₂₃ H ₂₈ N ₆ O ₃
268137	4-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268138	3-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268139	3(S)-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268140	3(R)-Me-1-Piz	C ₂₃ H ₂₈ N ₆ O ₃
268141	4-Et-1-Piz	C ₂₄ H ₃₀ N ₆ O ₃
268142	3,5-(Me)2-1-Piz	C ₂₄ H ₃₀ N ₆ O ₃
268143	3-(CH ₂ OH)-1-Piz	C ₂₃ H ₂₈ N ₆ O ₄
268144	3-[N(Me)2CH ₂]-1-Piz	C ₂₅ H ₃₃ N ₇ O ₃

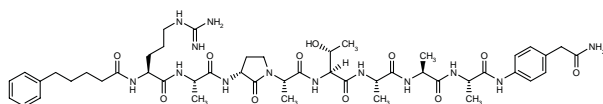
SOURCE – Celltech.

REFERENCES

1. Davis, P.D. et al. (Celltech Therapeutics Ltd.) *2-Pyrimidineamine derivs. and processes for their preparation.* WO 9818782.

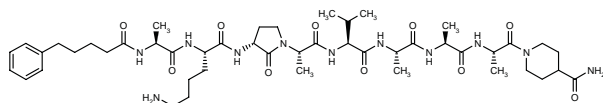
266206

2-[4-[2(*S*)-[3(*R*)-(5-Phenylpentanoyl-arginyl-alanyl-amino)-2-oxopyrrolidin-1-yl]propionyl-threonyl-alanyl-alanyl-alanyl-amino]phenyl]acetamide

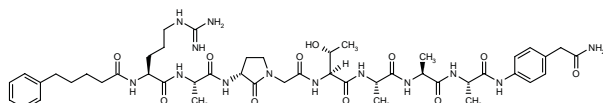


C₄₈H₇₁N₁₃O₁₁; Mol wt: 1006.1690

ACTION – Agent for the treatment of autoimmune diseases and inflammatory disorders such as rheumatoid arthritis and multiple sclerosis, a peptide that binds to major histocompatibility complex (MHC) class II molecules and inhibits T-cell activation by selfantigens characteristic of autoimmune diseases. *In vitro*, compound was found to bind to purified HLA-DR4Dw4 at a concentration of 0.1 µM or much less. *In vivo*, it was active in a delayed-type hypersensitivity model in mice when administered at a dose < 0.1 mg/kg/day using osmotic minipumps. Other specifically claimed peptides include the following:



267207: C₄₇ H₇₅ N₁₁ O₁₀



267208: C₄₇ H₆₉ N₁₃ O₁₁

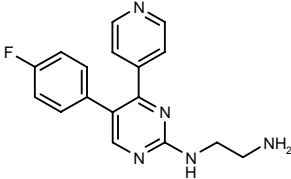
SOURCE – Zeneca.

REFERENCES

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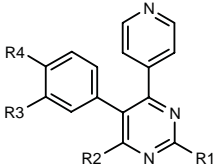
266222

*N*¹-[5-(4-Fluorophenyl)-4-(4-pyridyl)pyrimidin-2-yl]ethane-1,2-diamine

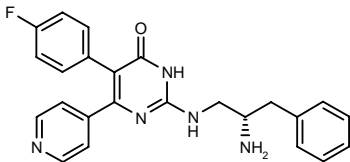


C17 H16 F N5; Mol wt: 309.3464

ACTION – An inhibitor of proinflammatory cytokines such as tumor necrosis factor (TNF-α), IL-1β, IL-6 and/or IL-8, with potential in the treatment of a broad range of conditions including rheumatoid arthritis, osteoporosis, osteoarthritis, pancreatic β-cell destruction, inflammatory bowel disease, psoriasis, allergic rhinitis, asthma, diabetes, Alzheimer’s disease, stroke, myocardial infarction, atherosclerosis, sepsis and myalgias caused by viral infections. Other specifically claimed compounds from this series of substituted pyrimidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
267315	1-pyrrolidinyl	H	H	F	C ₁₉ H ₁₇ FN ₄
267316	1-Piz	H	H	F	C ₁₉ H ₁₈ FN ₅
267317	2,6-(Cl)2-PhCH2	OH	H	F	C ₂₂ H ₁₄ Cl ₂ FN ₃ O
267318	SCH2CH2Ph	OH	H	F	C ₂₃ H ₁₈ FN ₃ OS
267319	(S)-NHCH2CH(NH2)CH2Ph	H	CF3	H	C ₂₅ H ₂₂ F ₃ N ₅
267320	(S)-NHCH2-CH(CH2Ph)N(Me)2	H	Me	H	C ₂₇ H ₂₉ N ₅
267321	(S)-1,2,3,4-tetrahydro-3-isoquinolyl-CH=N	H	CF3	H	C ₂₆ H ₂₀ F ₃ N ₅
267322	(S)-NHCH2CH(CH2Ph)-NHCOCH2NH2	H	CF3	H	C ₂₇ H ₂₆ F ₃ N ₆ O
267323	(S)-NHCH2CH(NH2)CH2Ph	H	Cl	F	C ₂₄ H ₂₁ ClFN ₅
267324	(S)-NHCH2CH(NH2)CH2Ph	H	F	H	C ₂₄ H ₂₂ FN ₅
267325	(S)-NHCH2CH(NH2)CH2Ph	H	H	Cl	C ₂₄ H ₂₂ ClN ₅



267327: C24 H22 F N5 O

SOURCE – Amgen.

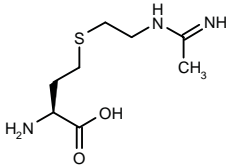
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1. Spohr, U.D. et al. (Amgen Inc.) *Substd. pyrimidine cpds. and their use.* WO 9824782.

269164

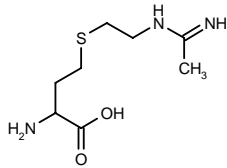
S-[2-(1-Iminoethylamino)ethyl]-L-homocysteine

2-(*S*)-Amino-7-(1-iminoethylamino)-5-thiaheptanoic acid



C8 H17 N3 O2 S; Mol wt: 219.3073

ACTION – Selective inhibitor of inducible nitric oxide synthase (iNOS; IC₅₀ = 0.73 μM) with > 500-fold selectivity over the endothelial isoform (eNOS; 53% inhibition at 300 μM) and about 300-fold selectivity over the neuronal isoform (nNOS; IC₅₀ = 220 μM). Following oral administration of 10 mg/kg to mice, it exhibited a bioavailability of 92%. Claimed for the treatment of arthritis, asthma, ileus and migraine. Other specifically claimed compounds include the following:



Compound	Isomer	Formula
269165	racemic	C ₈ H ₁₇ N ₃ O ₂ S
269166	R	C ₈ H ₁₇ N ₃ O ₂ S

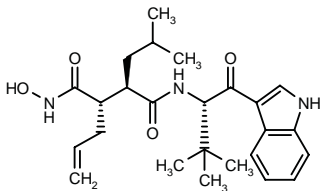
SOURCE – Glaxo Wellcome.

REFERENCES

1. Beams, R.M. et al. (Glaxo Wellcome plc) *Nitric oxide synthase inhibitors.* WO 9830537.

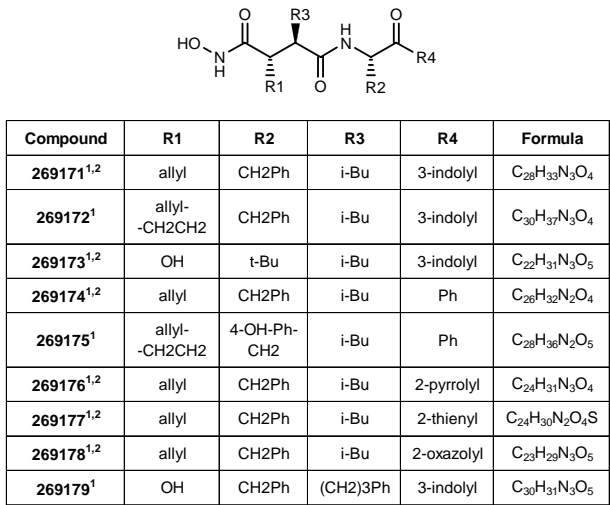
269170^{1,2}

2-(*S*)-Allyl-3(*R*)-[*N*-[1(*S*)-(1*H*-indol-3-ylcarbonyl)-2,2-dimethylpropyl]carbamoyl]-5-methylhexanehydroxamic acid



C25 H35 N3 O4; Mol wt: 441.5685

ACTION – An inhibitor of matrix metalloproteinases such as stromelysin (IC₅₀ = 1.2 nM), as well as the production of tumor necrosis factor-α (TNF-α), with potential in the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, gingivitis, corneal, epidermal or gastric ulceration, cancer, asthma, septic shock and inflammatory bowel disease. A representative compound from a series of C-terminal ketone hydroxamic acid derivatives, wherein the following are also included:



SOURCE – Abbott.

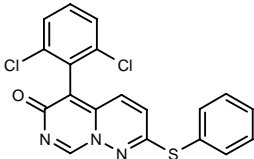
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1. Davidsen, S.K. et al. (Abbott Laboratories Inc.) *C-terminal ketone hydroxamic acid inhibitors of matrix metalloproteinases and TNFA secretion*. WO 9830541.

2. Sheppard, G.S. et al. *Aryl ketones as novel replacements for the C-terminal amide bond of succinyl hydroxamate MMP inhibitors*. Bioorg Med Chem Lett 1998, 8(22): 3251.

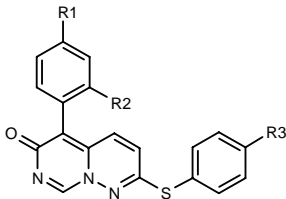
269180

5-(2,6-Dichlorophenyl)-2-(phenylsulfanyl)pyrimido[3,4-*b*]pyridazin-6-one



C19 H11 Cl2 N3 O S; Mol wt: 400.2879

ACTION – Agent for the treatment or prevention of inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attack, angiogenic disorders, organ hypoxia, vascular hyperplasia or cardiac hypertrophy, an inhibitor of p38 kinase. *In vitro*, it inhibited the ATPase activity of activated p38 with a K_i value of 0.4 μM, as well as the production of IL-6 and IL-8 in IL-1-stimulated human peripheral blood mononuclear cells (PBMCs; IC₅₀ = 0.60 and 0.85 μM, respectively). Additionally, compound was also shown to inhibit the expression of cyclooxygenase type 2 (COX-2) induced by lipopolysaccharide (LPS) in human PBMCs. A representative compound from a series of nitrogen-containing heterocycles, wherein the following are also included:



Compound	R1	R2	R3	Formula
269181	F	H	H	C ₁₉ H ₁₂ FN ₃ OS
269182	Cl	Cl	H	C ₁₉ H ₁₁ Cl ₂ N ₃ OS
269183	Cl	Cl	Me	C ₂₀ H ₁₃ Cl ₂ N ₃ OS

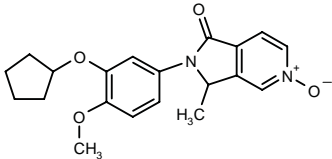
SOURCE – Vertex.

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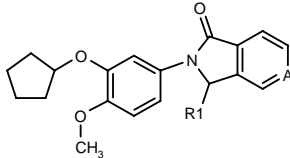
269236

2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one 5-oxide



C20 H22 N2 O4; Mol wt: 354.4038

ACTION – Agent for the treatment of inflammatory and autoimmune diseases such as rheumatoid arthritis, osteoarthritis, septic shock, asthma, graft-versus-host reaction, psoriasis, ulcerative colitis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus and chronic glomerulonephritis, an inhibitor of the production of tumor necrosis factor-α (TNF-α; 78% inhibition at 1 μM in lipopolysaccharide [LPS]-stimulated murine macrophages). *In vivo*, it gave 95% inhibition of LPS-induced TNF-α production in mice at 10 mg/kg p.o. LD₅₀ > 3.5 g/kg p.o. in mice. Other compounds from this series of 3,4-dialkoxyphenyl derivatives include the following:



Compound	R1	A	Formula
269237	Me	CH	C ₂₁ H ₂₃ NO ₃
269238	H	N	C ₁₉ H ₂₀ N ₂ O ₃
269239	Me	N	C ₂₀ H ₂₂ N ₂ O ₃
269240	H	N(O)	C ₁₉ H ₂₀ N ₂ O ₄

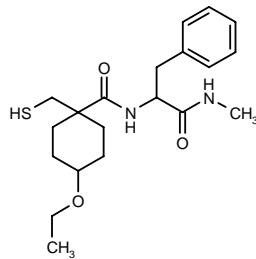
SOURCE – Dae Wong.

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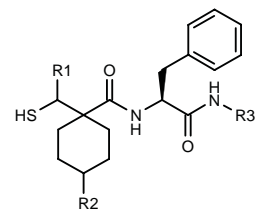
269273

N-[4-Ethoxy-1-(sulfanylmethyl)cyclohexylcarbonyl]-DL-phenylalanine methylamide



C20 H30 N2 O3 S; Mol wt: 378.5340

ACTION – Agent for the treatment of inflammatory conditions, osteoarthritis, rheumatoid arthritis and tumors that acts through the inhibition of matrix metalloproteinases, particularly collagenase 3, and tumor necrosis factor- α (TNF- α) production. Other specifically claimed cyclic thio substituted acylaminoacid amide derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
269274	H	OMe	Ph	cis	C ₂₄ H ₃₀ N ₂ O ₃ S
269275	CH ₂ CH ₂ Ph	H	Me		C ₂₆ H ₃₄ N ₂ O ₂ S
269276	H	OEt	Me	cis	C ₂₀ H ₃₀ N ₂ O ₃ S

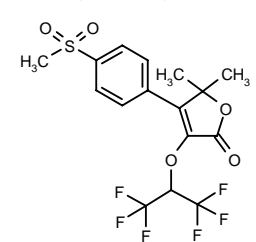
SOURCE – Novartis.

REFERENCES

1. Fink, C.A. (Novartis AG) *Certain cyclic thio subst. acylaminoacid amide derivs.* WO 9842662.

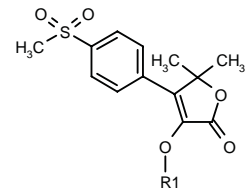
269327

5,5-Dimethyl-4-[4-(methylsulfonyl)phenyl]-3-[2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]furan-2(5H)-one



C16 H14 F6 O5 S; Mol wt: 432.3356

ACTION – Antiinflammatory and analgesic agent, a potent and selective inhibitor of cyclooxygenase type 2 (COX-2), as demonstrated using transfected CHO cells expressing human COX-2 (IC₅₀ = 0.04 μ M) and against lipopolysaccharide (LPS)-induced PGE₂ formation in human whole blood (IC₅₀ < 0.4 μ M). *In vivo*, compound inhibited carrageenan-induced rat paw edema with an ED₅₀ value of 1.0 mg/kg p.o. Within this series of 4-(sulfonylphenyl)-2(5H)-furanones, the following are also included:



Compound	R1	Formula
269328	ethynyl-CH(Me)	C ₁₇ H ₁₈ O ₅ S
269329	CH(Me)CH ₂ Br	C ₁₆ H ₁₈ BrO ₅ S
269330	(S)-CH ₂ CH(Me)CH ₂ OH	C ₁₇ H ₂₂ O ₆ S
269331	(R)-CH ₂ CH(Me)CH ₂ F	C ₁₇ H ₂₁ FO ₅ S
269332	(S)-CH ₂ CH(Me)CH ₂ F	C ₁₇ H ₂₁ FO ₅ S
269333	4,4-(F)2-cyclohexyl	C ₁₉ H ₂₂ F ₂ O ₅ S
269334	1-(CH ₂ F)-cyclopropyl-CH ₂	C ₁₈ H ₂₁ FO ₅ S

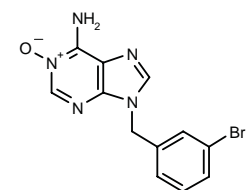
SOURCE – Merck Frosst.

REFERENCES

1. Leblanc, Y. et al. (Merck Frosst Canada Inc.) *(Methylsulfonyl)phenyl-2-(5H)-furanones with oxygen link as COX-2 inhibitors.* WO 9841516.

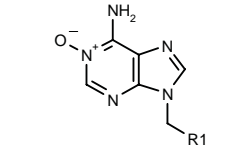
269339

9-(3-Bromobenzyl)adenine-*N*¹-oxide



C12 H10 Br N5 O; Mol wt: 320.1490

ACTION – Antiinflammatory and immunomodulating agent that acts by inhibiting cell adhesion and the expression of adhesion molecules. *In vitro*, compound inhibited the tumor necrosis factor- α (TNF- α)-stimulated adhesion of HL-60 cells to human umbilical vein endothelial cells (HUVEC) with an IC₅₀ value of 0.157 μ M. In addition, it was found to inhibit the expression of ICAM-1 and E-selectin in HUVEC cultures stimulated with TNF- α . *In vivo* activity was demonstrated in the adjuvant arthritis model in the rat at 0.5 mg/kg/day p.o. x 17 days. Other compounds from this series of adenine-1-*N*-oxide derivatives include the following:



Compound	R1	Formula
269340	1-Naph	C ₁₆ H ₁₃ N ₅ O
269341	3-Cl-Ph	C ₁₂ H ₁₀ ClN ₅ O
269342	2,3-(Cl)2-Ph	C ₁₂ H ₉ Cl ₂ N ₅ O
269343	3-CF ₃ -Ph	C ₁₃ H ₁₀ F ₃ N ₅ O

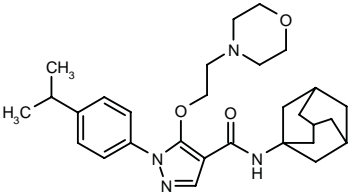
SOURCE – Japan Energy.

REFERENCES

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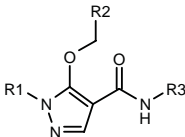
269391

N-(1-Adamantyl)-1-(4-isopropylphenyl)-5-[2-(4-morpholinyl)ethoxy]pyrazole-4-carboxamide



C29 H40 N4 O3; Mol wt: 492.6600

ACTION – Cannabinoid CB₂ receptor agonist with potential in the treatment of immune and inflammatory disorders such as rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, psoriasis, eczema, multiple sclerosis and ankylosing spondylitis, as well as diabetes, gout, osteoporosis and renal ischemia. Within this series of pyrazole derivatives, the following are also specifically claimed:



Compound	R1	R2	R3	Formula
269392	4-F-Ph	4-Pyr	2-adamantyl	C ₂₆ H ₂₇ FN ₄ O ₂
269393	4-Cl-Ph	1-Me-2-Pip	3-noradamantyl	C ₂₆ H ₃₃ ClN ₄ O ₂
269394	CH ₂ Ph	4-morpholinyl-CH ₂	1-adamantyl	C ₂₇ H ₃₆ N ₄ O ₃
269395	4-MeO-Ph	4-F-Ph	2-adamantyl	C ₂₈ H ₃₀ FN ₃ O ₃
269396	4-Cl-Ph	Ph	3-noradamantyl	C ₂₆ H ₂₆ ClN ₃ O ₂
269397	4-F-Ph	4-Pyr	1-adamantyl	C ₂₆ H ₂₇ FN ₄ O ₂
269398	4-Cl-Ph	1-Me-2-Pip	1-adamantyl	C ₂₇ H ₃₅ ClN ₄ O ₂
269399	Ph	4-Pyr	1-adamantyl	C ₂₆ H ₂₈ N ₄ O ₂

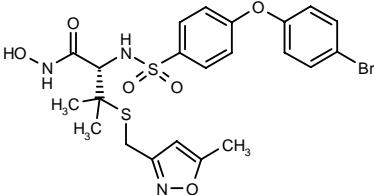
SOURCE – SmithKline Beecham.

REFERENCES

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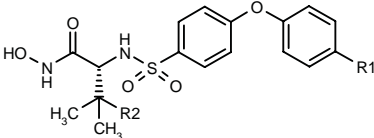
269468

2(S)-[4-(4-Bromophenoxy)phenylsulfonamido]-3-methyl-3-(5-methylisoxazol-3-ylmethylsulfanyl)butyrohydroxamic acid



C22 H24 Br N3 O6 S2; Mol wt: 570.4826

ACTION – A potent inhibitor of matrix metalloproteinases such as human stromelysin (K_i = 0.24 nM), human collagenase 3 (K_i = 0.013 nM) and human gelatinase (K_i = 0.007 nM), and also of tumor necrosis factor- α (TNF- α) production, claimed for use in the treatment of tumor growth, invasion or metastasis, rheumatoid arthritis, osteoporosis, multiple sclerosis and other conditions associated with the degradation of protein components of extracellular matrix tissues including cartilage, bone, tendons and skin. Other representative compounds include the following:



Compound	R1	R2	Formula
269469	Br	2-Pyr-CH ₂ S	C ₂₃ H ₂₄ BrN ₃ O ₅ S ₂
269470	Cl	Me	C ₁₈ H ₂₁ ClN ₂ O ₅ S

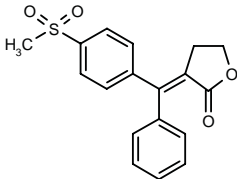
SOURCE – Agouron.

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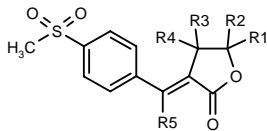
269556

3-[1-[4-(Methylsulfonyl)phenyl]-1-phenylmethylene]tetrahydrofuran-2-one

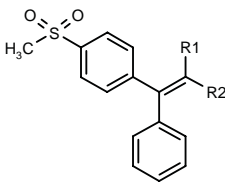


C18 H16 O4 S; Mol wt: 328.3864

ACTION – Antiinflammatory agent, a selective inhibitor of cyclooxygenase type 2 (COX-2). Other specifically claimed compounds from this series of α -methylene γ -lactones include the following:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
269557	Me	Me	H	H	Ph	E	C ₂₀ H ₂₀ O ₄ S
269559	H	H	H	H	3-F-Ph	Z	C ₁₈ H ₁₅ FO ₄ S
269560	Me	H	H	H	Ph	E	C ₁₉ H ₁₈ O ₄ S
269561	Me	Me	H	H	4-F-Ph	E	C ₂₀ H ₁₉ FO ₄ S
269562	Me	Me	H	H	3-F-Ph	Z	C ₂₀ H ₁₉ FO ₄ S
269563	Me	Me	H	H	2-Pyr	Z	C ₁₉ H ₁₉ NO ₄ S
269564	Me	Me	H	H	4-Cl-Ph	Z	C ₂₀ H ₁₉ ClO ₄ S
269565	H	H	Me	Me	Ph		C ₂₀ H ₂₀ O ₄ S
269568	Me	Me	H	H	3-Pyr	Z	C ₁₉ H ₁₉ NO ₄ S
269569	Me	Me	H	H	4-Pyr	Z	C ₁₉ H ₁₉ NO ₄ S



Compound	R1,R2	Formula
269566	-(CH2)4-	C ₁₉ H ₂₀ O ₂ S
269567	-(CH2)3CO-	C ₁₉ H ₁₈ O ₃ S
269570	-(CH2)3-	C ₁₈ H ₁₈ O ₂ S

SOURCE – Merck Frosst.

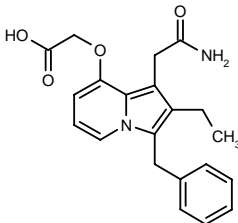
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120-1032

267663

2-[1-(2-Amino-2-oxoethyl)-3-benzyl-2-ethylindolizin-8-yloxy]acetic acid



C21 H22 N2 O4; Mol wt: 366.4148

M.p. 213-8 °C (decomp.).

ACTION – Inhibitor of human secretory phospholipase A₂ (hs-PLA₂; IC₅₀ = 0.013 μM in a chromogenic assay) with potential in the treatment of inflammatory conditions such as septic shock, acute pancreatitis, rheumatoid arthritis, bronchial asthma, allergic rhinitis and respiratory distress syndrome.

SOURCE – Shionogi.

REFERENCES

1. Dillard, R.D. et al. (Eli Lilly and Company;Shionogi & Co. Ltd.) *Indolizine sPLA₂ inhibitors*. JP 98505584, WO 9603383.

2. Hagishita, S. et al. *Potent inhibitors of secretory phospholipase A₂: Synthesis and inhibitory activities on indolizine and indene derivatives*. J Med Chem 1996, 39(19): 3636.

3. Kitadokoro, K. et al. *Crystal structure of human secretory phospholipase A₂-IIA complex with the potent indolizine inhibitor 120-1032*. J Biochem 1998, 123(4): 619.

ETANERCEPT

USAN

213242

1-235-Tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G₁ (human γ₁-chain Fc fragment)

TNFR:Fc
TNR-001

ACTION – Antiarthritic agent, a recombinant dimeric fusion protein that acts by specifically binding to tumor necrosis factor (TNF; both TNF-α and TNF-β), competitively inhibiting the binding of TNF to the TNF receptor (TNFR) and thereby inhibiting its activity.

INDICATION – Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).

PRESENTATION – Single-use vials containing lyophilized powder for parenteral administration following reconstitution, 25 mg.

PROPRIETARY NAME – Enbrel® (US).

SOURCES – Immunex; Wyeth-Ayerst.

RECENT REFERENCES

1. Baumgartner, S.W. et al. *Response of elderly patients to TNF receptor P75 Fc fusion protein (TNFR:Fc; Enbrel(TM)).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 160.

2. Garrison, L. et al. *Longterm safety and efficacy of TNF receptor (P75) Fc fusion protein (TNFR:Fc; Enbrel(TM)) in DMARD refractory rheumatoid arthritis (RA).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 1987.

3. Garrison, L. et al. *Safety and efficacy of tumor necrosis factor receptor P75 Fc fusion protein (TNFR:Fc; Enbrel(TM)) in polyarticular course juvenile rheumatoid arthritis.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 584.

4. Moreland, L. et al. *Functioning and well-being of DMARD-failed rheumatoid arthritis in patients receiving P75 TNFR:Fc (Enbrel(TM)).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 159.

5. Moreland, L.W. et al. *Effects of TNF receptor (P75) fusion protein (TNFR:Fc; Enbrel(TM)) on immune function.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 158.

6. Moreland, L.W. et al. *Longterm treatment of DMARD failing rheumatoid arthritis patients with TNF receptor p75 Fc fusion protein (TNFR:Fc; Enbrel(TM)).* J Invest Med 1998, 46(3): 229A.

7. Moreland, L.W. et al. *Optimal dose of TNF receptor P75 Fc fusion protein (TNFR:Fc; Enbrel(TM)).* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 157.

8. Moreland, L.W. et al. *Phase III trial of DMARD failing rheumatoid arthritis patients with TNF receptor p75 Fc fusion protein (TNFR:Fc; Enbrel(TM)).* J Invest Med 1998, 46(3): 228A.

9. Sander, O. and Rau, R. *Treatment of refractory rheumatoid arthritis with a tumor necrosis factor alpha receptor fusion protein (TNFR55-IgG1)- A monocentric observation in 80 patients.* Z Rheumatol 1998, 57(5): 307.

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11. *Advisory committee unanimously recommends approval for Enbrel.* Prous Science Daily Essentials 1998, Sept 17.

12. *Enbrel BLA accepted for review and assigned priority review status.* Prous Science Daily Essentials 1998, June 25.

13. *Enbrel development status.* Immunex Corp. Company Communication 1998, July 15

14. *Enbrel efficacy demonstrated in juvenile RA patients.* Prous Science Daily Essentials 1998, Sept 7.

15. *Enbrel prescribing information.* Immunex Corp. Product Fact Sheet 1998, Nov 3.

16. *Enbrel safety established in juvenile RA patients; efficacy data now being generated.* Prous Science Daily Essentials 1998, March 17.

17. *European filing announced for Enbrel.* Prous Science Daily Essentials 1998, Nov 11.

18. *Favorable results obtained with Enbrel combination in RA.* Prous Science Daily Essentials 1998, March 16.

19. *FDA advisory committee meeting scheduled to review Enbrel BLA.* Prous Science Daily Essentials 1998, Aug 25.

20. *FDA approves, Immunex launches breakthrough treatment for RA.* Prous Science Daily Essentials 1998, Nov 3.

21. *Immunex completes BLA submission for Enbrel.* Prous Science Daily Essentials 1998, May 8.

22. *Immunex completes filing of its biological license application for Enbrel(TM) for potential treatment of rheumatoid arthritis.* Immunex Corp. Press Release 1998, May 7.

23. *Immunex drug Enbrel(TM) recommended for approval by FDA advisory committee for treatment of rheumatoid arthritis.* Immunex Corp. Press Release 1998, Sept 16.

24. *Immunex files sBLA for Enbrel as treatment for juvenile rheumatoid arthritis.* Prous Science Daily Essentials 1998, Nov 27.

25. *Immunex's Enbrel(TM) receives designation as "Fast Track Product".* Immunex Corp. Press Release 1998, March 17.

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*Drug Data Report 1998, 020(04): 0344.

LEFLUNOMIDE+

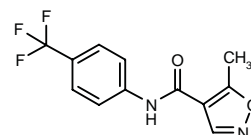
Rec INN

116061

5-Methyl-N-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide

HWA-486

RS-34821



C12 H9 F3 N2 O2; Mol wt: 270.2091

ACTION – Isoxazole immunomodulating agent that inhibits dihydroorotate dehydrogenase, an enzyme involved in *de novo* pyrimidine synthesis, and has antiproliferative activity. Its activity is mainly due to the active metabolite A-771726.

INDICATION – Treatment of active rheumatoid arthritis in adults to reduce signs and symptoms and delay structural damage as evidenced by X-ray erosions and joint space narrowing.

PRESENTATION – Tablets, 10 and 20 mg (maintenance), and 100 mg (3-day loading dose).

PROPRIETARY NAME – Arava (US).

SOURCE – Hoechst Marion Roussel.

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2. Herrmann, M.L. et al. *The primary mode of action of leflunomide in rheumatoid arthritis is inhibition of de novo pyrimidine synthesis.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 17.

3. Moreland, L.W. et al. *Efficacy of leflunomide vs placebo vs methotrexate in early and late rheumatoid arthritis.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 733.

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5. Scott, D.L. et al. *Efficacy of leflunomide vs placebo vs sulfasalazine in rheumatoid arthritis: Effect of disease duration.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 735.

6. Schiff, M. et al. *X-Ray analysis of 12 months treatment of active rheumatoid arthritis with leflunomide compared to placebo or methotrexate.* 62nd Natl Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 736.

7. Silva, H.T. et al. *Molecular mechanisms of the immunosuppressive effect of leflunomide in vivo: Inhibition of dihydroorotate dehydrogenase (DHODH).* 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 9.

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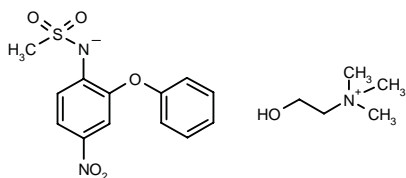
*Drug Data Rep 1986, 08(02): 0117.

NIMESULIDE CHOLINE SALT

269004

N-(4-Nitro-2-phenxyphenyl)methanesulfonamide (2-hydroxyethyl)trimethylammonium salt

N-(4-Nitro-2-phenxyphenyl)methanesulfonamide choline salt



C13 H11 N2 O5 S . C5 H14 N O; Mol wt: 411.4765

ACTION – A novel salt of the known antiinflammatory agent nimesulide⁺ with high water solubility and high stability in aqueous solution, as well as good bioavailability. Suitable for parenteral administration.

SOURCE – Dompé.

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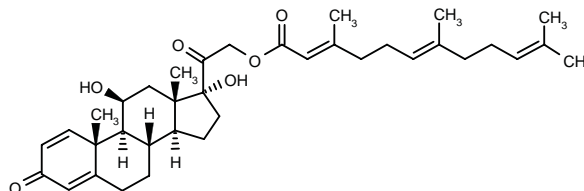
*Drug Data Rep 1986, 08(11): 1000.

PREDNISOLONE FARNESYLATE⁺

154424

11 β ,17 α -Dihydroxy-21-[3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatrienoyloxy]pregna-1,4-diene-3,20-dione

PNF-21



C36 H50 O6; Mol wt: 578.7850

ACTION – Antiinflammatory agent.

INDICATION – Treatment of swelling and pain of the finger, hand and elbow joints associated with rheumatoid arthritis.

PRESENTATION – Gel, 14 mg/g in tubes of 25 and 50 g.

PROPRIETARY NAMES – *Farnerate Gel* (Taiho-JP); *Farnezone Gel* (Dainippon Pharmaceutical, Kuraray-JP).

SOURCES – Dainippon Pharmaceutical (manufactured by Kuraray); Taiho.

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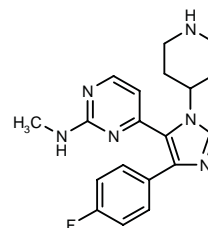
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*Drug Data Report 1990, 012(02): 0097.

SB-226882

267795

4-[4-(4-Fluorophenyl)-1-(4-piperidinyl)-1*H*-imidazol-5-yl]-*N*-methylpyrimidine-2-amine



C19 H21 F N6; Mol wt: 352.4149

ACTION – Potent and selective inhibitor of p38/CSBP MAP kinase with improved antiinflammatory properties compared to its precursor SB-203580 but devoid of significant interactions with cytochrome P-450 isozymes, in contrast to the latter. p38 MAP kinase inhibitors reduce the production of proinflammatory cytokines and block early signaling events in the disease process and therefore have potential to alter the underlying pathophysiology of acute and chronic inflammation.

SOURCE – SmithKline Beecham.

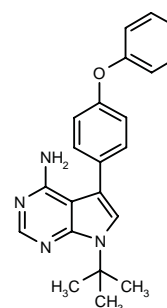
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IMMUNOMODULATING AGENTS

269277

7-*tert*-Butyl-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-ylamine



C22 H22 N4 O; Mol wt: 358.4428

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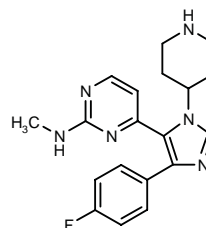
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*Drug Data Report 1990, 012(02): 0097.

SB-226882

267795

4-[4-(4-Fluorophenyl)-1-(4-piperidinyl)-1*H*-imidazol-5-yl]-*N*-methylpyrimidine-2-amine



C₁₉ H₂₁ F N₆; Mol wt: 352.4149

ACTION – Potent and selective inhibitor of p38/CSBP MAP kinase with improved antiinflammatory properties compared to its precursor SB-203580 but devoid of significant interactions with cytochrome P-450 isozymes, in contrast to the latter. p38 MAP kinase inhibitors reduce the production of proinflammatory cytokines and block early signaling events in the disease process and therefore have potential to alter the underlying pathophysiology of acute and chronic inflammation.

SOURCE – SmithKline Beecham.

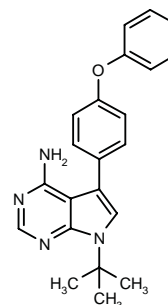
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- Adams, J.L. et al. *p38 MAP kinase inhibitors: Progress, pitfalls and possibilities.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst C.5.

IMMUNOMODULATING AGENTS

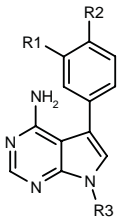
269277

7-*tert*-Butyl-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-ylamine



C₂₂ H₂₂ N₄ O; Mol wt: 358.4428

ACTION – Agent for the treatment of proliferative diseases and disorders of the immune system that inhibits one or more of the tyrosine kinases of the Src and Syk families ($IC_{50} < 5\text{ }\mu\text{M}$ against Lck kinase). Within this series of specifically claimed pyrrolo[2,3-*d*]pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269278	H	SO2Ph	t-Bu	C ₂₂ H ₂₂ N ₄ O ₂ S
269279	H	NHSO2Ph	i-Pr	C ₂₁ H ₂₁ N ₅ O ₂ S
269280	H	4-(AcNH)-PhO	t-Bu	C ₂₄ H ₂₅ N ₅ O ₂
269281	H	3-CO2H- -4-NO2-PhO	i-Pr	C ₂₂ H ₁₉ N ₅ O ₅
269282	H	OPh	2-OH-cyclopentyl	C ₂₃ H ₂₂ N ₄ O ₂
269283	OMe	NHCOPh	cyclopentyl	C ₂₅ H ₂₅ N ₅ O ₂
269284	OH	NHSO2Ph	cyclopentyl	C ₂₃ H ₂₃ N ₅ O ₃ S
269285	OH	4-Cl-PhCONH	cyclopentyl	C ₂₄ H ₂₂ ClN ₅ O ₂
269286	H	2-(t-BuCONH)- -4-NO2-PhO	H	C ₂₃ H ₂₂ N ₆ O ₄

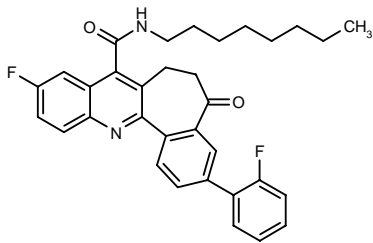
SOURCE – Knoll.

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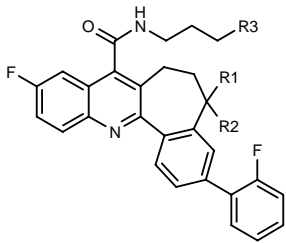
269376

10-Fluoro-3-(2-fluorophenyl)-*N*-octyl-5-oxo-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxamide



C33 H32 F2 N2 O2; Mol wt: 526.6238

ACTION – Immunosuppressive agent, as demonstrated by 51.4% inhibition of plaque-forming cells in spleen from sensitized mice at a concentration of 10 μM . A representative compound from a series of tetracyclic quinolines, wherein the following are also included:



Compound	R1	R2	R3	Formula
269377	-O-		H	C ₂₈ H ₂₂ F ₂ N ₂ O ₂
269378	-O-		Me	C ₂₉ H ₂₄ F ₂ N ₂ O ₂
269379	-O-		Pr	C ₃₁ H ₂₈ F ₂ N ₂ O ₂
269380	OH	H	Me	C ₂₉ H ₂₆ F ₂ N ₂ O ₂
269381	OH	H	C5H11	C ₃₃ H ₃₄ F ₂ N ₂ O ₂
269382	H	H	H	C ₂₈ H ₂₄ F ₂ N ₂ O
269383	H	H	Me	C ₂₉ H ₂₆ F ₂ N ₂ O
269384	H	H	Pr	C ₃₁ H ₃₀ F ₂ N ₂ O
269385	H	H	C5H11	C ₃₃ H ₃₄ F ₂ N ₂ O

SOURCE – Kyowa Hakko.

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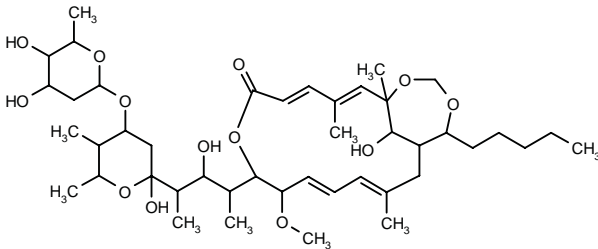
ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

FORMAMICIN

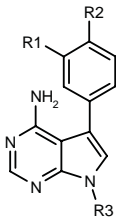
269296

8-[3-[4-(4,5-Dihydroxy-6-methyltetrahydrofuran-2-yloxy)-2-hydroxy-5,6-dimethyltetrahydropyran-2-yl]-2-hydroxy-1-methylbutyl]-20-hydroxy-9-methoxy-1,3,13-trimethyl-16-pentyl-7,17,19-trioxabicyclo[13.3.1]nonadeca-2,4,10,12-tetraen-6-one



C44 H72 O13; Mol wt: 809.0398

ACTION – Agent for the treatment of proliferative diseases and disorders of the immune system that inhibits one or more of the tyrosine kinases of the Src and Syk families ($IC_{50} < 5\text{ }\mu\text{M}$ against Lck kinase). Within this series of specifically claimed pyrrolo[2,3-*d*]pyrimidine derivatives, the following are also included:



Compound	R1	R2	R3	Formula
269278	H	SO2Ph	t-Bu	C ₂₂ H ₂₂ N ₄ O ₂ S
269279	H	NHSO2Ph	i-Pr	C ₂₁ H ₂₁ N ₅ O ₂ S
269280	H	4-(AcNH)-PhO	t-Bu	C ₂₄ H ₂₅ N ₅ O ₂
269281	H	3-CO2H- -4-NO2-PhO	i-Pr	C ₂₂ H ₁₉ N ₅ O ₅
269282	H	OPh	2-OH-cyclopentyl	C ₂₃ H ₂₂ N ₄ O ₂
269283	OMe	NHCOPh	cyclopentyl	C ₂₅ H ₂₅ N ₅ O ₂
269284	OH	NHSO2Ph	cyclopentyl	C ₂₃ H ₂₃ N ₅ O ₃ S
269285	OH	4-Cl-PhCONH	cyclopentyl	C ₂₄ H ₂₂ ClN ₅ O ₂
269286	H	2-(t-BuCONH)- -4-NO2-PhO	H	C ₂₃ H ₂₂ N ₆ O ₄

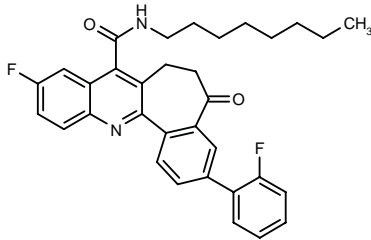
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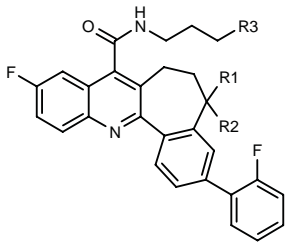
269376

10-Fluoro-3-(2-fluorophenyl)-*N*-octyl-5-oxo-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxamide



C33 H32 F2 N2 O2; Mol wt: 526.6238

ACTION – Immunosuppressive agent, as demonstrated by 51.4% inhibition of plaque-forming cells in spleen from sensitized mice at a concentration of 10 μM . A representative compound from a series of tetracyclic quinolines, wherein the following are also included:



Compound	R1	R2	R3	Formula
269377	-O-		H	C ₂₈ H ₂₂ F ₂ N ₂ O ₂
269378	-O-		Me	C ₂₉ H ₂₄ F ₂ N ₂ O ₂
269379	-O-		Pr	C ₃₁ H ₂₈ F ₂ N ₂ O ₂
269380	OH	H	Me	C ₂₉ H ₂₆ F ₂ N ₂ O ₂
269381	OH	H	C5H11	C ₃₃ H ₃₄ F ₂ N ₂ O ₂
269382	H	H	H	C ₂₈ H ₂₄ F ₂ N ₂ O
269383	H	H	Me	C ₂₉ H ₂₆ F ₂ N ₂ O
269384	H	H	Pr	C ₃₁ H ₃₀ F ₂ N ₂ O
269385	H	H	C5H11	C ₃₃ H ₃₄ F ₂ N ₂ O

SOURCE – Kyowa Hakko.

REFERENCES

1. Nakajo, I. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Tetracyclic quinoline derivs*. JP 98231289.

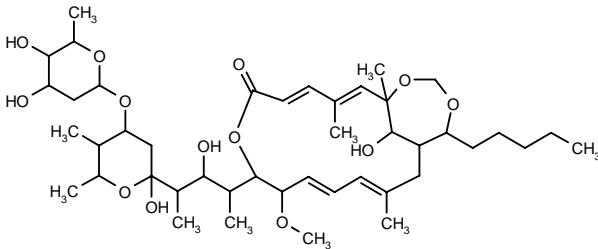
ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

FORMAMICIN

269296

8-[3-[4-(4,5-Dihydroxy-6-methyltetrahydrofuran-2-yloxy)-2-hydroxy-5,6-dimethyltetrahydropyran-2-yl]-2-hydroxy-1-methylbutyl]-20-hydroxy-9-methoxy-1,3,13-trimethyl-16-pentyl-7,17,19-trioxabicyclo[13.3.1]nonadeca-2,4,10,12-tetraen-6-one



C44 H72 O13; Mol wt: 809.0398

ACTION – Antifungal and antineoplastic antibiotic isolated from *Saccharothrix* sp. MK27-91F2 (FERM P-16053), active against *Saccharomyces cerevisiae* F-7 (MIC = 0.2 µg/ml) and *Cryptococcus miyabeanus* (MIC = 0.39 µg/ml) and proven to be extremely potent *in vitro* against various tumor cell lines including mouse leukemia P388 (IC₅₀ = 0.00013 µg/ml), mouse sarcoma S180 (IC₅₀ = 0.00345 µg/ml) and mouse Ehrlich ascites tumor cells (IC₅₀ = 0.00026 µg/ml).

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

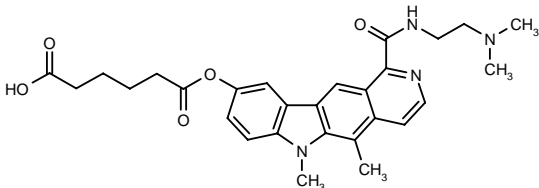
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DNA-INTERCALATING DRUGS

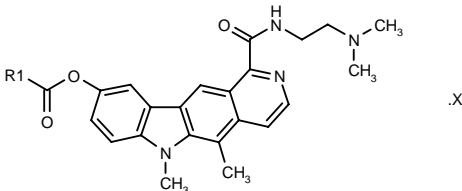
268352

9-(5-Carboxypentanoyloxy)-N-[2-(dimethylamino)ethyl]-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide



C28 H32 N4 O5; Mol wt: 504.5838

ACTION – Antineoplastic agent with potent *in vitro* cytotoxicity against murine leukemia P388, murine Lewis lung carcinoma and human epidermoid carcinoma KB-3-1 cells (IC₅₀ = 5.1, 3.5 and 40.6 nM, respectively), being comparable in potency to doxorubicin (IC₅₀ = 18.1, 19.3 and 17.3 nM, respectively); when tested against the doxorubicin-resistant KB-A1 subline, it was found to be about 9-fold more potent than doxorubicin (IC₅₀ = 757.9 nM vs. 6693 nM). *In vivo*, it increased survival time of mice bearing P388 leukemia, with T/C x 100 values on day 60 of 154 and 236%, respectively, when given at 40 mg/kg i.v. on day 1 and 40 mg/kg i.v. on days 1, 5 and 9; in this test, compound was well tolerated at doses up to 320 mg/kg i.v. Antitumor activity was additionally shown in nude mice bearing human lung carcinoma NCI-H460 xenografts (T/C x 100 = 147% at 80 mg/kg i.v. on days 7 and 14). Other compounds from this series of ellipticine derivatives include the following:



Compound	R1	X	Formula
268353	Me		C ₂₄ H ₂₆ N ₄ O ₃
268354	(CH ₂) ₃ CO ₂ H	2HCl	C ₂₇ H ₃₀ N ₄ O ₅ ·2HCl

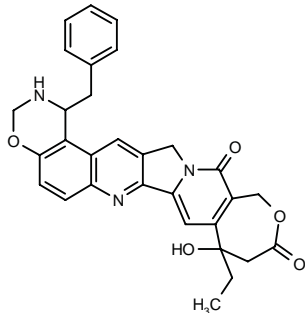
SOURCE – ADIR.

REFERENCES

1. Guillonneau, C. et al. (ADIR et Cie.) *Ellipticine derivs., their preparation and pharmaceutical compsns. containing them*. EP 850940.

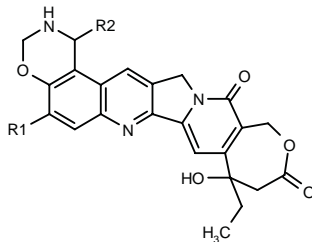
268953

1-Benzyl-9-ethyl-9-hydroxy-2,3,10,11,14,16-hexahydro-1H,9H,13H-[1,3]oxazino[5,6-f]oxepino[3',4':6,7]-indolizino[1,2-b]quinoline-11,14-dione

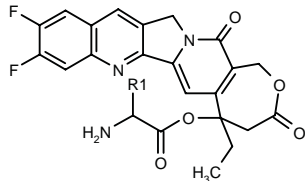


C30 H27 N3 O5; Mol wt: 509.5593

ACTION – Antineoplastic and antiviral agent, an analog of camptothecin shown to induce a concentration-dependent inhibition of topoisomerase I-induced relaxation of DNA with a potency higher than that of the parent compound. Other specifically claimed camptothecin prodrugs and analogs include the following:



Compound	R1	R2	Formula
268954	H	Et	C ₂₅ H ₂₅ N ₃ O ₅
268955	H	Me	C ₂₄ H ₂₃ N ₃ O ₅
268956	F	CH ₂ Ph	C ₃₀ H ₂₆ FN ₃ O ₅



Compound	R1	Formula
270167	H	C ₂₃ H ₁₉ F ₂ N ₃ O ₅
270168	Me	C ₂₄ H ₂₁ F ₂ N ₃ O ₅

SOURCE – SCRAS.

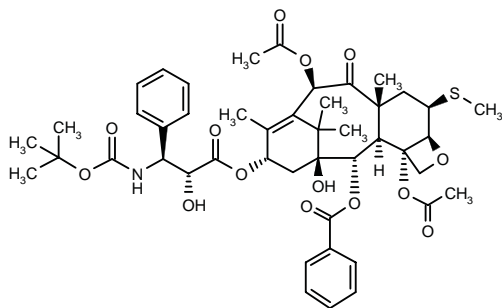
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ANTIMITOTIC DRUGS

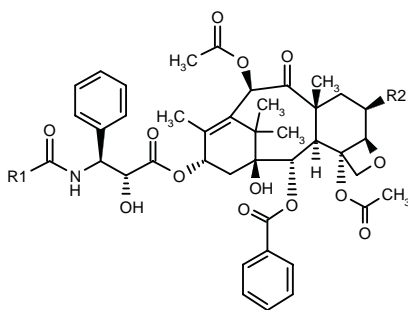
268882

[2a*R*-[2aα,3β,4aβ,6β,9α(2*R*,3*S*),11β,12α,12aα,12bα]]-6,12b-Diacetoxy-12-benzoyloxy-9-[3-(*tert*-butoxy-carbonylamino)-2-hydroxy-3-phenylpropionyloxy]-11-hydroxy-4a,8,13,13-tetramethyl-3-(methylsulfanyl)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]-benz[1,2-*b*]oxet-5-one



C46 H57 N O14 S; Mol wt: 880.0153

ACTION – Antineoplastic agent, a paclitaxel derivative with particularly potent *in vitro* cytotoxicity against human colon cancer HCT116 cells (IC₅₀ = 0.2 nM). It was active *in vivo* in mice bearing sarcoma M5067 tumors (optimal dose: 13 mg/kg/day i.v. on days 1, 3, 5, 7 and 9 post-implantation). Within this series of 6-thio substituted paclitaxel derivatives, the following are also included:



Compound	R1	R2	Formula
268883	t-BuO	SOMe	C ₄₆ H ₅₇ NO ₁₅ S
268884	OEt	SMe	C ₄₄ H ₅₃ NO ₁₄ S
268885	Ph	SEt	C ₄₉ H ₅₉ NO ₁₃ S
268886	Ph	vinyl-S	C ₄₉ H ₅₃ NO ₁₃ S
268887	Ph	SPh	C ₅₃ H ₅₅ NO ₁₃ S

SOURCE – Bristol-Myers Squibb.

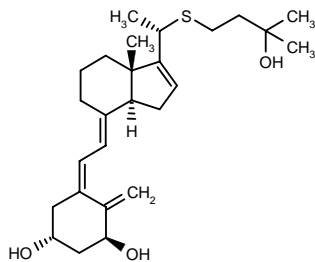
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HORMONAL AGENTS

268841

1α,25-Dihydroxy-16,17-didehydro-23-thiavitamin D₃



C26 H40 O3 S; Mol wt: 432.6650

ACTION – Antiproliferative and antiinflammatory agent, a vitamin D analog with high affinity for vitamin D receptors and negligible calcemic activity, as demonstrated in mice following administration of 30 μg/kg i.v.

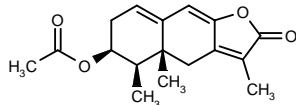
SOURCE – Chugai.

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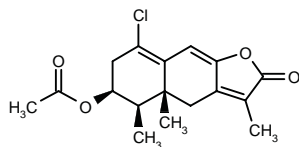
268989

[4a*R*-(4aα,5α,6α)]-6-Acetoxy-3,4a,5-trimethyl-2,4,4a,5,6,7-hexahydronaphtho[2,3-*b*]furan-2-one

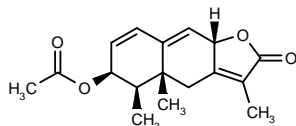


C17 H20 O4; Mol wt: 288.3410

ACTION – Nonsteroidal antiprogesterone that acts by inhibiting the binding of progesterone to its receptor (IC₅₀ < 100 nM) and is expected to be free of the side effects associated with steroid inhibitors. Potentially useful for the treatment of certain cancers such as breast or ovarian cancer, uterine myoma, endometriosis, meningioma, myeloma, osteoporosis and other menopausal disturbances, as well as for use as an abortifacient or oral contraceptive. Other compounds from this series of sesquiterpene derivatives include the following:



268990: C17 H19 Cl O4



268991: C17 H20 O4

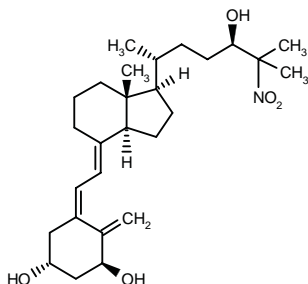
SOURCE – Meiji Seika.

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1. Harimaya, K. et al. (Meiji Seika Kaisha, Ltd.) *Sesquiterpene derivs. having progesterone receptor binding inhibitory activity*. US 5817816.

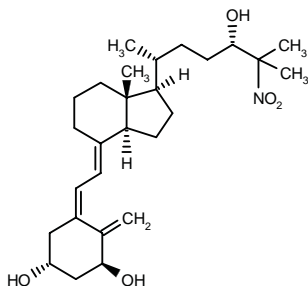
269707

1 α ,24(*R*)-Dihydroxy-25-nitrovitamin D₃



C27 H43 N O5; Mol wt: 461.6387

ACTION – Vitamin D derivative with similar affinity to 1 α ,25-dihydroxyvitamin D₃ for vitamin D receptors and potent differentiation-inducing activity in HL-60 cells (90.5% of cells differentiated at a concentration of 0.1 μ M). Another compound from this series of 1 α ,24-dihydroxy-25-nitrovitamin D₃ derivatives is:



269708: C27 H43 N O5

SOURCE – Teijin.

REFERENCES

1. Okamoto, M. et al. (Teijin Ltd.) *1 α ,24-Dihydroxy-25-nitro-vitamin D3 derivs. and their preparation method*. JP 98265453.

CANCER IMMUNOTHERAPY

TRASTUZUMAB⁺

198466

Immunoglobulin G1 (human–mouse monoclonal rhuMab HER2 γ 1-chain anti-human p185^{c-erbB2} receptor), disulfide with human–mouse monoclonal rhuMab HER2 light chain, dimer

Anti-HER2

ACTION – Monoclonal antibody that binds to a protein called HER2 (human epidermal growth factor receptor 2), bioengineered from part of a mouse antibody that is altered to closely resemble a human antibody.

INDICATION – Treatment of metastatic breast cancer in patients with tumors overexpressing the HER2 protein, in combination with paclitaxel in first-line treatment and as monotherapy in second- and third-line treatment.

PRESENTATION – Vials containing lyophilized powder for i.v. administration, 440 mg.

PROPRIETARY NAME – Herceptin (US).

SOURCES – Genentech; Roche.

RECENT REFERENCES

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12. Pegram, M. et al. *Phase II study of intravenous recombinant humanized anti-p185 HER-2 monoclonal antibody (rhuMab HER-2) plus cisplatin in patients with HER-2/neu overexpressing metastatic breast cancer*. Proc Amer Soc Clin Oncol 1995, Abst 124.
13. Pegram, M.D. et al. *Antibody dependent cell-mediated cytotoxicity in breast cancer patients in phase III clinical trials of humanized anti-HER2 antibody*. Proc Amer Assoc Cancer Res 1997, Abst 4044.
14. Slamon, D. et al. *Addition of Herceptin(TM) (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2+/MBC) markedly increases anticancer activity: A randomized, multinational controlled phase III trial*. Proc Amer Soc Clin Oncol 1998, Abst 377.
15. Slivkowski, M.X. et al. *A humanized monoclonal antibody for the treatment of HER2 overexpressing breast cancer*. Proc Amer Assoc Cancer Res 1996, 625.
16. *Biotechnology breakthrough in breast cancer wins FDA approval. New therapy for a quarter of women with metastatic breast cancer, testing for protein overexpression critical*. Genentech, Inc. Press Release 1998, Sept 25.
17. *Favorable phase III trial results reported for HER2 monoclonal antibody*. Prous Science Daily Essentials 1997, Dec 31.
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19. *Genentech begins shipping Herceptin to U.S. oncologists*. Prous Science Daily Essentials 1998, Oct 30.
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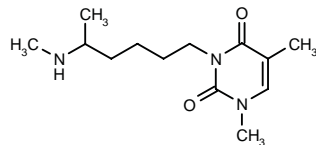
MONOGRAPH – Sorbera, L.A. and Rabasseda, X. *Trastuzumab.* Drugs Fut 1998, 023(10): 1078.

*Drug Data Report 1998, 020(07): 0627.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

268207

1,5-Dimethyl-3-[5-(methylamino)hexyl]pyrimidine-2,4(1*H*,3*H*)-dione



C13 H23 N3 O2; Mol wt: 253.3437

ACTION – Agent capable of inhibiting abnormal intracellular signaling mediated through the IL-1 type 1 receptor that exerts its activity by inhibiting lyso-PA acyltransferase (LPAAT) and/or phosphatidate phosphohydrolase (PAPH). Potentially useful for the treatment or prevention of sepsis, hematopoietic or organ toxicity,

cancer, AIDS and AIDS-related conditions, alopecia caused by chemotherapy, and inflammatory or autoimmune diseases.

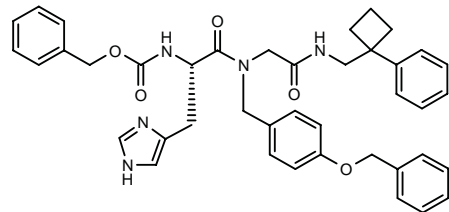
SOURCE – Cell Therapeutics.

REFERENCES

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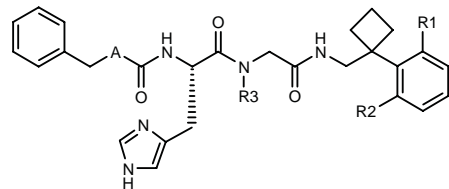
269133

Benzyloxycarbonyl-L-histidyl-[*N*-(4-benzyloxybenzyl)]glycine 1-phenylcyclobutylmethylamide

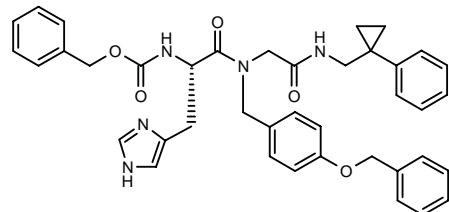


C41 H43 N5 O5; Mol wt: 685.8207

ACTION – Antineoplastic agent, an inhibitor of protein farnesyltransferase (IC_{50} = 0.006 and 0.075 μ M, respectively, in HEPES buffer with or without K_3PO_4). It exhibited a minimum effective dose (MED) of 0.02 μ M for inhibition of Ras farnesylation in a gel shift assay, as well as an IC_{50} value of 0.047 μ M in a clonogenic assay using H61 (H-*ras*-transformed NIH3T3) cells. Antitumor activity was tested *in vivo* in nude mice bearing H61 xenografts, where it produced 73 and 100% inhibition of tumor growth, respectively, when given at 96 mg/kg s.c. b.i.d. x 14 days or 23 mg/kg i.p. b.i.d. x 14 days. Within this series of cycloalkyl derivatives, the following are also included:



Compound	R1	R2	R3	A	Formula
269135	H	H	4-(2-Pyr-CH2O)-PhCH2	O	C ₄₀ H ₄₂ N ₆ O ₅
269136	H	H	4-Me-PhCH2	O	C ₃₅ H ₃₉ N ₅ O ₄
269137	H	H	4-(PhCH2O)-PhCH2	O	C ₄₂ H ₄₅ N ₅ O ₅
269138	H	H	4-MeO-PhCH2	O	C ₃₅ H ₃₉ N ₅ O ₅
269139	H	H	4-Me-PhCH2	N(Me)	C ₃₆ H ₄₂ N ₆ O ₃
269140	H	H	4-(PhCH2O)-PhCH2	N(Me)	C ₄₂ H ₄₆ N ₆ O ₄
269141	Cl	Cl	4-(PhCH2O)-PhCH2	O	C ₄₁ H ₄₁ Cl ₂ N ₅ O ₅
269142	H	H	CH2CH=CHMe	O	C ₃₁ H ₃₇ N ₅ O ₄
269143	H	H	Pr	O	C ₃₀ H ₃₇ N ₅ O ₄
269144	H	H	(R)-CH(Me)Ph	O	C ₃₅ H ₃₉ N ₅ O ₄



269134: C40 H41 N5 O5

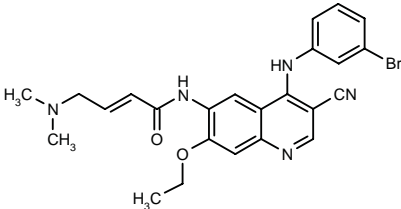
SOURCE – Warner-Lambert.

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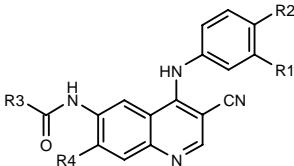
269592

N-[4-(3-Bromophenylamino)-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)-2-butenamide

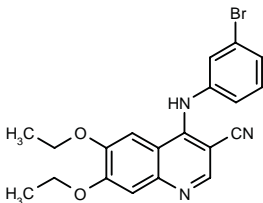


C24 H24 Br N5 O2; Mol wt: 494.3906

ACTION – An inhibitor of protein tyrosine kinases such as epidermal growth factor (EGF) receptor tyrosine kinase (IC₅₀ = 0.0006 μM), with potential in the treatment of cancer and polycystic kidney disease. Compound exhibited potent growth-inhibitory effects in a wide range of human tumor cells *in vitro*. *In vivo*, it was found to inhibit the growth of human epidermoid A431 tumors implanted in nude mice, giving a T/C x 100 value at day 28 following tumor implantation of 19 and 21%, respectively, when given at 80 mg/kg i.p. or p.o. on days 1, 5 and 9. Other specifically claimed compounds from this series of substituted 3-cyanoquinolines include the following:



Compound	R1	R2	R3	R4	Formula
269593	Cl	F	CH=CHCH2N(Me)2	OMe	C ₂₃ H ₂₁ ClFN ₅ O ₂
269594	Cl	F	CH=CHCH2N(Et)2	OMe	C ₂₅ H ₂₅ ClFN ₅ O ₂
269595	Br	F	CH=CHCH2N(Me)2	OMe	C ₂₃ H ₂₁ BrFN ₅ O ₂
269597	Br	H	CH=CHCH2N(Et)2	OEt	C ₂₆ H ₂₈ BrN ₅ O ₂
269598	Cl	F	4-morpholinyl-CH2CH=CH	OMe	C ₂₅ H ₂₃ ClFN ₅ O ₃
269599	Br	H	CH=CHCH2N(Me)2	OMe	C ₂₃ H ₂₂ BrN ₅ O ₂
269600	Br	H	MeOCH2-ethynyl	H	C ₂₁ H ₁₅ BrN ₄ O ₂
269601	Cl	F	CH=CHCH2N(Me)2	H	C ₂₂ H ₁₉ ClFN ₅ O



269596: C20 H18 Br N3 O2

SOURCE – American Home Products.

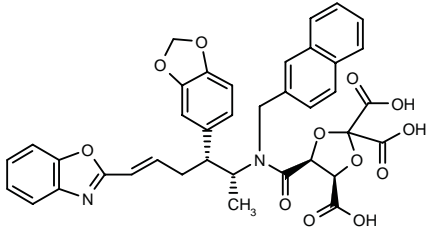
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J-104871*

252065

5(S)-[N-[2(R)-(1,3-Benzodioxol-5-yl)-5-(2-benzoxazolyl)-1(R)-methyl-4(E)-pentenyl]-N-(2-naphthylmethyl)carbamoyl]-1,3-dioxolane-2,2,4(R)-tricarboxylic acid



C38 H32 N2 O12; Mol wt: 708.6728

ACTION – Antineoplastic agent, a potent, selective and competitive inhibitor of rat brain protein farnesyltransferase (IC₅₀ = 3.9 nM; IC₅₀ geranylgeranyltransferase-I = 0.6 μM); it also selectively inhibited Ras processing in activated H-ras-transformed NIH 3T3 cells (IC₅₀ = 3.1 μM). *In vivo*, compound suppressed tumor growth in nude mice transplanted with activated H-ras-transformed NIH 3T3 cells, producing 28 and 52% inhibition, respectively, at doses of 40 and 80 mg/kg/day i.p.

SOURCE – Banyu.

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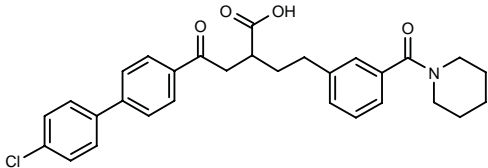
2. Yonemoto, M. et al. *J-104,871, a novel farnesyltransferase inhibitor, blocks ras farnesylation in vivo in a farnesyl pyrophosphate-competitive manner*. Mol Pharmacol 1998, 54(1): 1.

*Identified compound **252065** Drug Data Report 1997, 019(09): 0840.

ANTIANGIOGENIC AGENTS

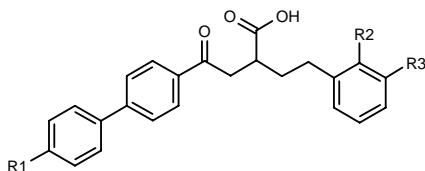
268196

4-(4'-Chlorobiphenyl-4-yl)-4-oxo-2-[2-[3-(piperidin-1-ylcarbonyl)phenyl]ethyl]butyric acid



C30 H30 Cl N O4; Mol wt: 504.0230

ACTION – An inhibitor of matrix metalloproteinases (MMPs) such as gelatinase A (MMP-2; K_i = 10.3 nM), gelatinase B (MMP-9; K_i = 58.1 nM) and stromelysin (MMP-3; K_i = 34.4 nM), with potential in the treatment of MMP-mediated disorders such as tumor metastasis, osteoarthritis, rheumatoid arthritis, periodontal disease and corneal ulceration. Other related compounds include the following:



Compound	R1	R2	R3	Formula
268197	Cl	1-Pip-CO	H	C ₃₀ H ₃₀ ClNO ₄
268198	Cl	CON(Me)-CH ₂ CO ₂ Et	H	C ₃₀ H ₃₀ ClNO ₆
268199	Cl	H	4-morpholinyl-CO	C ₂₉ H ₂₈ ClNO ₅
268200	Cl	H	CON(Me)-CH ₂ CO ₂ Et	C ₃₀ H ₃₀ ClNO ₆
268201	OCH ₂ Ph	H	1-Pip-CO	C ₃₇ H ₃₇ NO ₅

SOURCE – Bayer.

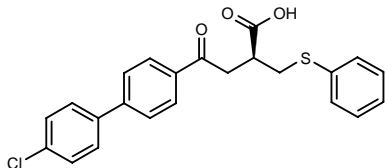
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BAY-12-9566*

238610

4-(4'-Chlorobiphenyl-4-yl)-4-oxo-2(S)-(phenylsulfanylmethyl)butyric acid



C23 H19 Cl O3 S; Mol wt: 410.9191

ACTION – Potent, orally active biphenyl matrix metalloproteinase (MMP) inhibitor with potent activity against recombinant MMP-2 (gelatinase A; K_i = 11 nM), MMP-9 (gelatinase B; K_i = 301 nM) and MMP-3 (stromelysin 1; K_i = 134 nM), but no activity against MMP-1 (interstitial collagenase; K_i > 5000 nM), shown to inhibit HT1080 tumor cell invasion by 38-66% at a concentration of 1 μM in an *in vitro* invasion assay, without inhibiting cell proliferation or motility; inhibition of angiogenesis was also demonstrated *in vivo* in mice following oral administration. It was found to suppress both primary tumor growth and metastases in several models in mice such as human colon carcinoma HCT116, human breast cancer MDA-MB-435, murine B16 melanoma and Lewis lung carcinoma. Currently in phase II/III trials in cancer patients as monotherapy and in combination with cytotoxic agents. It was also shown to inhibit cartilage lesion development in dog and guinea pig models of osteoarthritis, and clinical trials are in progress to examine its potential in human osteoarthritis.

SOURCE – Bayer.

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10. Grochow, L. et al. *Phase I and pharmacokinetic study of the matrix metalloproteinase inhibitor (MMPI), BAY12-9566.* Proc Amer Soc Clin Oncol 1998, Abst 822.

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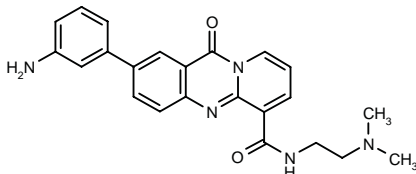
MONOGRAPH – Sorbera, L.A. et al. *Bay-12-9566.* Drugs Fut 1999, 024(01): in preparation.

*Identified compound **238610** (see **237976**) Drug Data Report 1996, 018(09): 0824.

OTHER ANTINEOPLASTIC AGENTS

266194

2-(3-Aminophenyl)-*N*-[2-(dimethylamino)ethyl]-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamide



C23 H23 N5 O2; Mol wt: 401.4677

ACTION – Antineoplastic agent with *in vitro* cytotoxicity against cisplatin-sensitive human ovarian adenocarcinoma A2780 and cisplatin-resistant A2780 cells (IC_{50} = 0.40 and 3.70 μ g/ml, respectively). *In vivo* it was effective against murine leukemia P388, although it was less active than vincristine (ILS = 57% at 200 mg/kg i.p. vs. 114% for vincristine at 0.8 mg/kg i.p.); when tested in animals bearing murine colon 26 tumors, compound was found to be less active than doxorubicin (ILS = 35% at 250 mg/kg i.p. vs. 71% for doxorubicin at 4 mg/kg i.p.). Compound also exhibited tumor growth-inhibitory activity in nude mice bearing human LS174T xenografts, giving a T/C x 100 value of 59% at day 28 after tumor implantation when given at 250 mg/kg i.p., whereas vincristine at 1.0 mg/kg i.p. gave a T/C x 100 value of 52%.

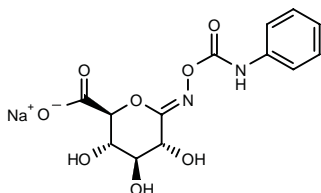
SOURCE – American Home Products.

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268992

(*Z*)-1-Deoxy-1-(*N*-phenylcarbamoyloxyimino)-D-glucopyranuronic acid sodium salt



C13 H13 N2 Na O8; Mol wt: 348.2417

ACTION – An inhibitor of human β -glucuronidase (IC_{50} = 0.6 μ M), potentially useful for the suppression of tumor growth and metastasis, as well as for the treatment of inflammatory disorders.

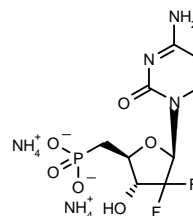
SOURCE – Hoechst Marion Roussel.

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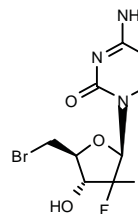
269214

2',5'-Dideoxy-2',2'-difluorocytidin-5'-ylphosphonic acid diammonium salt



C9 H12 F2 N3 O6 P . 2 H3 N; Mol wt: 361.2402

ACTION – Antiviral and antineoplastic agent with cytotoxic activity against the human leukemia cell line CCRF-CEM (IC_{50} = 0.3 μ g/ml) and antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2). Another representative compound within this series of specifically claimed difluoronucleoside phosphonic acid derivatives is:



270169: C9 H10 Br F2 N3 O3

SOURCE – Lilly.

REFERENCES

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ELF3

265154

Polypeptide from the human ETS family

ACTION – Human polypeptide from the ETS family that has been shown to be upregulated in epithelial tumors such as mammary and prostate tumors and is thus expected to be useful in the diagnosis and treatment of these cancers. Also provided are variants and derivatives thereof, polynucleotides encoding them, as well as antibodies, agonists and antagonists of this polypeptide.

SOURCE – SmithKline Beecham.

REFERENCES

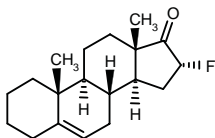
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FLUASTERONE*

141530

16 α -Fluoroandrost-5-en-17-one

8354



C19 H27 F O; Mol wt: 290.4193

ACTION – Orally active, synthetic dehydroepiandrosterone (DHEA) analog that retains the pharmacological activity of DHEA but is devoid of hepatotoxicity and androgenic effects. Currently undergoing phase I clinical trials as a preventive treatment for breast cancer and also potentially useful for the treatment of autoimmune diseases and type II diabetes.

SOURCE – Aeson Therapeutics.

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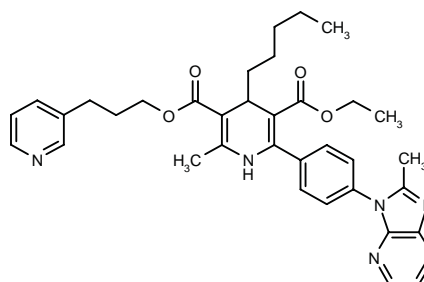
17. RCT forms company to develop pharmaceuticals from synthetic DHEA. Research Corporation Technologies Press Release 1995, Dec 11.

*Identified compound 141530 (see 138734) Drug Data Report 1988, 010(06): 0512.

RESISTANCE MODIFIERS

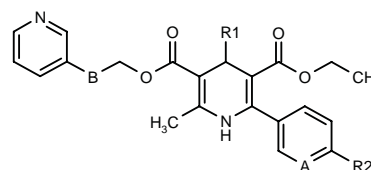
266185

2-Methyl-6-[4-(2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]-4-pentyl-1,4-dihydropyridine-3,5-dicarboxylic acid 5-ethyl 3-[3-(3-pyridyl)propyl] diester



C36 H41 N5 O4; Mol wt: 607.7509

ACTION – Multidrug resistance modifier, a dihydropyridine derivative shown to be more potent than verapamil in enhancing doxorubicin and vincristine cytotoxicity against multidrug-resistant VJ-300 cells. Potentiating effects were also observed *in vivo* in mice bearing vincristine-resistant leukemia, the T/C x 100 value for vincristine being 96% at 100 μ g/kg i.p. x 5 days in the absence of test compound and 127% when combined with 100 mg/kg of test compound using the same dose schedule. The compound was much less potent than verapamil and nicardipine in inhibiting KCl-induced rat aorta contractions (IC_{50} > 30.0 μ M vs. 0.26 μ M for nicardipine and 1.43 μ M for verapamil). Other compounds from this series of 1,4-dihydropyridines include the following:



Compound	R1	R2	A	B	Formula
266981	i-Pr	2-Me-1 <i>H</i> -imidazo-[4,5- <i>b</i>]pyridin-1-yl	CH	-CH2CH2-	C ₃₄ H ₃₇ N ₅ O ₄
266982	i-Pr	2-Me-1 <i>H</i> -imidazo-[4,5- <i>c</i>]pyridin-1-yl	CH	-CH2CH2-	C ₃₄ H ₃₇ N ₅ O ₄
266983	C5H11	H	CH	-CH2CH2-	C ₂₉ H ₃₆ N ₂ O ₄
266984	C5H11	H	N	-CH2CH2-	C ₂₈ H ₃₆ N ₃ O ₄
266985	C5H11	2-Me-1 <i>H</i> -imidazo-[4,5- <i>c</i>]pyridin-1-yl	CH(E)	-CH=CH-	C ₃₆ H ₃₉ N ₅ O ₄
266986	CH2CH2Ph	2-Me-1 <i>H</i> -imidazo-[4,5- <i>c</i>]pyridin-1-yl	CH(E)	-CH=CH-	C ₃₈ H ₃₇ N ₅ O ₄
266987	(E)-CH=CHPh	1-imidazolyl	CH	-CH2CH2-	C ₃₅ H ₃₄ N ₄ O ₄

SOURCE – Nikken Chemicals.

REFERENCES

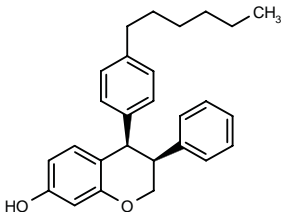
- Tasaka, S. et al. (Nikken Chemicals Co., Ltd.) *1,4-Dihydropyridine derivs.* JP 98204061, WO 9823607.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

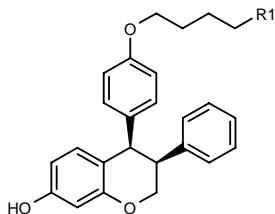
265112

(±)-*cis*-4-(4-Hexylphenyl)-3-phenyl-3,4-dihydro-2*H*-1-benzopyran-7-ol



C27 H30 O2; Mol wt: 386.5320

ACTION – Estrogen agonist with potential in the treatment of estrogen-related disorders, preferably the treatment or prevention of bone loss and osteoporosis. Other compounds from this series of *cis*-3,4-chroman derivatives include the following:



Compound	R1	Formula
266631	4-morpholinyl-CH2CH2	C31H37NO4
266632	CH2CH2N(Bu)2	C36H47NO3
266633	4-morpholinyl-(CH2)6	C36H48NO4
266634	4-morpholinyl	C29H33NO4

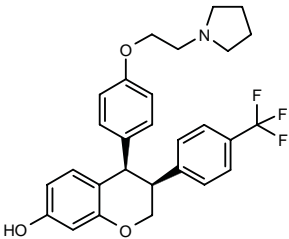
SOURCE – Novo Nordisk.

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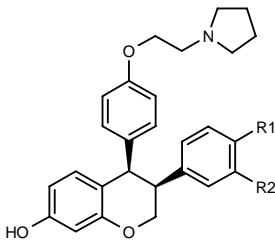
265113

(+)-*cis*-4-[4-[2-(1-Piperidinyl)ethoxy]phenyl]-3-[4-(trifluoromethyl)phenyl]-3,4-dihydro-2*H*-1-benzopyran-7-ol



C28 H28 F3 N O3; Mol wt: 483.5272

ACTION – Estrogen agonist with potential in the treatment of estrogen-related disorders, preferably the treatment or prevention of bone loss and osteoporosis. Other compounds from this series of *cis*-3,4-chroman derivatives include the following:



Compound	R1	R2	Isomer	Formula
268151	Me	H	+	C28H31NO3
268152	H	OH	+	C27H29NO4
268153	CF3	H	-	C28H28F3NO3
268154	Me	H	-	C28H31NO3
268155	H	OH	-	C27H29NO4
268156	F	H	racemic	C27H28FNO3

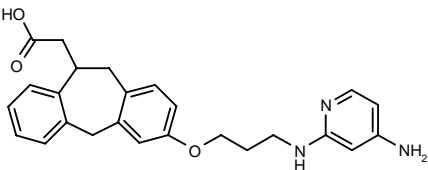
SOURCE – Novo Nordisk.

REFERENCES

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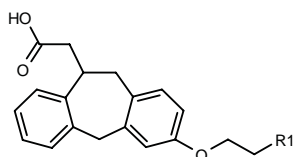
269167

(±)-2-[3-[3-(4-Amino-2-pyridylamino)propoxy]-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-10-yl]acetic acid



C25 H27 N3 O3; Mol wt: 417.5063

ACTION – Agent for the treatment of osteoporosis, inflammation, cancer and cardiovascular disorders such as atherosclerosis and restenosis, a potent and selective vitronectin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptor antagonist. Other specifically claimed tricyclic compounds include the following:



Compound	R1	Formula
269168	6-(EtNH)-2-Pyr	C ₂₆ H ₂₈ N ₂ O ₃
269169	4-Me-2-Pyr-NHCH ₂	C ₂₆ H ₂₈ N ₂ O ₃

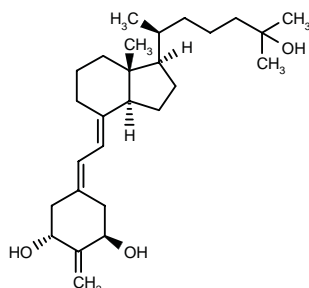
SOURCE – SmithKline Beecham.

REFERENCES

1. Miller, W.H. et al. (SmithKline Beecham Corp.) *Vitronectin receptor antagonists*. WO 9830542.

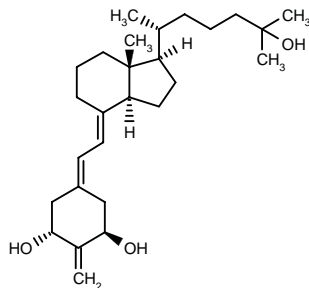
269229

(20S)-1 α ,25-Dihydroxy-2-methylene-19-norvitamin D₃



C27 H44 O3; Mol wt: 416.6416

ACTION – Agent for the treatment of osteoporosis, a vitamin D analog characterized by low intestinal calcium transport activity and high bone calcium mobilization activity. Also claimed for use in the treatment of psoriasis due to its high cell differentiation-inducing activity. Another specifically claimed 2-alkylidene-19-nor-vitamin D compound is:



269230: C27 H44 O3

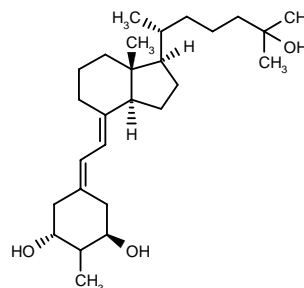
SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

REFERENCES

1. DeLuca, H.F. and Sicinski, R.R. (Wisconsin Alumni Research Foundation) *2-Alkylidene-19-nor-vitamin D cpds*. US 5843928, WO 9841501.

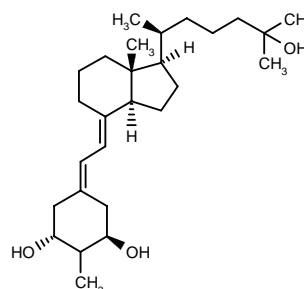
269231

1 α ,25-Dihydroxy-2-methyl-19-norvitamin D₃



C27 H46 O3; Mol wt: 418.6574

ACTION – Agent for the treatment of osteoporosis, a vitamin D analog characterized by low intestinal calcium transport activity and high calcium mobilization activity. Also claimed for use in the treatment of psoriasis due to its marked cell differentiation-inducing activity. Another representative compound within this series of 2-alkyl-19-nor-vitamin D compounds is:



269232: C27 H46 O3

SOURCE – Wisconsin Alumni Research Foundation, Madison, WI (US).

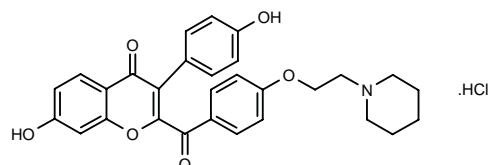
REFERENCES

1. DeLuca, H.F. and Sicinski, R.R. (Wisconsin Alumni Research Foundation) *2-Alkyl-19-nor-vitamin D cpds*. WO 9841500.

CHF-3316.01

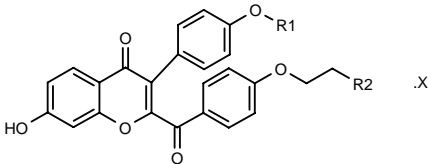
268734

7-Hydroxy-3-(4-hydroxyphenyl)-2-[4-[2-(1-piperidinyloxy)benzoyl]-4H-1-benzopyran-4-one hydrochloride



C29 H27 N O6 . HCl; Mol wt: 521.9942

ACTION – Agent for the treatment of osteoporosis that both inhibits bone resorption and stimulates the process of bone formation. Antiresorptive activity was demonstrated *in vitro* in rat fetal long bone cultures (24.81, 37.86 and 100% inhibition of ⁴⁵Ca²⁺ release at 3, 10 and 30 µM, respectively), being about 5-fold more potent than the most active metabolite of ipriflavone. The estrogen receptor binding affinity was determined in calf uterus preparations (K_i = 3.9 ± 0.3 nM; K_i tamoxifen = 6.8 nM). At dose levels of 10 and 20 mg/kg s.c., it induced 63 and 78% suppression, respectively, of the estradiol-induced increase in uterine weight in immature rats, but was devoid of uterotrophic effects. Other exemplified isoflavone derivatives include the following:



Compound	R1	R2	X	Formula
CHF-3290.01 [268735]	Me	1-Pip	HCl	C ₃₀ H ₂₉ NO ₆ .HCl
CHF-3340.01 [268736]	Me	1-Piz	2HCl	C ₂₈ H ₂₈ N ₂ O ₆ .2HCl
CHF-3356.01 [268737]	H	1-Piz	2HCl	C ₂₆ H ₂₆ N ₂ O ₆ .2HCl

SOURCE – Chiesi.

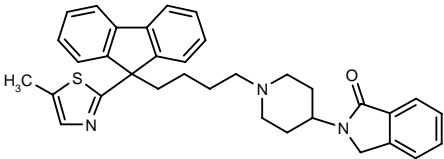
REFERENCES

1. Chiesi, P. et al. (Chiesi Farmaceutici SpA) *Isoflavone derivs., processes for the preparation thereof and pharmaceutical compsns. containing them.* WO 9829403.

TREATMENT OF LIPOPROTEIN DISORDERS

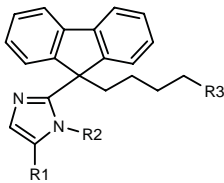
268858

2-[1-[4-[9-(5-Methyl-2-thiazolyl)-9*H*-fluoren-9-yl]butyl]-piperidin-4-yl]-2,3-dihydro-1*H*-isoindol-1-one

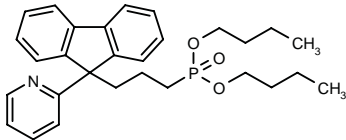


C34 H35 N3 O S; Mol wt: 533.7365

ACTION – Hypolipidemic and antiatherosclerotic agent, an inhibitor of microsomal triglyceride transfer protein (MTP), which catalyzes the transport of lipid molecules between phospholipid membranes and is expected to play a role in lipid metabolism. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
268859	H	Me	PO(OBu) ₂	C ₂₉ H ₃₉ N ₂ O ₃ P
268860	H	Me	4-(PhCONH)-Ph	C ₃₄ H ₃₁ N ₃ O
268861	H	Me	4-(1,3-dioxo-2-isoindoliny)-Ph	C ₃₅ H ₂₉ N ₃ O ₂
268862	Et	Me	4-(PhCONH)-1-Pip	C ₃₅ H ₄₀ N ₄ O
268863	Et	Me	4-(2-PhO-PhCONH)-1-Pip	C ₄₁ H ₄₄ N ₄ O ₂
268864	H	Et	4-(2-PhO-PhCONH)-1-Pip	C ₄₀ H ₄₂ N ₄ O ₂



268865: C29 H36 N O3 P

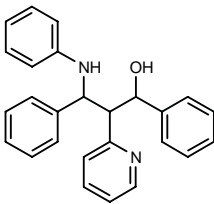
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Tino, J.A. (Bristol-Myers Squibb Co.) *Heterocyclic inhibitors of microsomal triglyceride transfer protein and method.* WO 9827979.

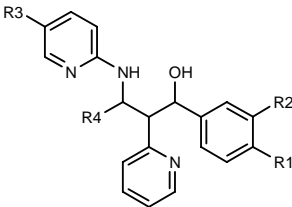
269017

1,3-Diphenyl-3-(phenylamino)-2-(2-pyridyl)-1-propanol



C26 H24 N2 O; Mol wt: 380.4886

ACTION – Hypolipidemic agent, an ileal bile acid transport inhibitor from a series of propanolamine derivatives, wherein the following are also included:



Compound	R1	R2	R3	R4	Formula
269018	H	H	H	3-thienyl	C ₂₃ H ₂₁ N ₃ OS
269019	H	H	OMe	Ph	C ₂₆ H ₂₅ N ₃ O ₂
269020	H	H	OEt	Ph	C ₂₇ H ₂₇ N ₃ O ₂
269021	H	H	H	2-NH2-Ph	C ₂₆ H ₂₄ N ₄ O
269022	H	H	H	2-OH-Ph	C ₂₆ H ₂₃ N ₃ O ₂
269023	H	H	H	3-OH-Ph	C ₂₆ H ₂₃ N ₃ O ₂
269024	H	OMe	H	Ph	C ₂₆ H ₂₅ N ₃ O ₂
269025	OMe	H	H	Ph	C ₂₆ H ₂₅ N ₃ O ₂
269026	H	H	H	2-(HOCH2CH2O)-Ph	C ₂₇ H ₂₇ N ₃ O ₃

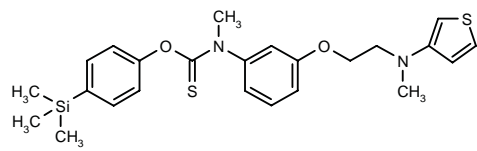
SOURCE – Hoechst Marion Roussel.

REFERENCES

1. Glombik, H. et al. (Hoechst Marion Roussel Deutschland GmbH) *Hypolipidemic propanol amine derivatives*. EP 869121, JP 98287651.

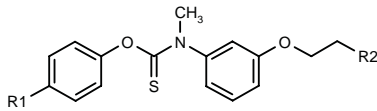
269156

N-Methyl-*N*-[3-[2-[*N*-methyl-*N*-(3-thienyl)amino]-ethoxy]phenyl]thiocarbamic acid *O*-[4-(trimethylsilyl)phenyl] ester



C24 H30 N2 O2 S2 Si; Mol wt: 470.7310

ACTION – Hypocholesterolemic and hypolipidemic agent that prevents cholesterol biosynthesis by virtue of its ability to inhibit squalene epoxidase (IC₅₀ = 4.0 nM in rat liver homogenates). Other representative compounds within this series of thiocarbamic acid derivatives include the following:



Compound	R1	R2	Formula
269157	t-Bu	3-thienyl-N(Me)CH2	C ₂₆ H ₃₂ N ₂ O ₂ S ₂
269158	t-Bu	CH2N(Me)Ph	C ₂₈ H ₃₄ N ₂ O ₂ S
269159	t-Bu	3-thienyl-CH2N(Me)	C ₂₆ H ₃₂ N ₂ O ₂ S ₂
269160	t-Bu	3-thienyl-N(Me)	C ₂₅ H ₃₀ N ₂ O ₂ S ₂
269161	C(Me)2OMe	3-thienyl-N(Me)	C ₂₅ H ₃₀ N ₂ O ₃ S ₂
269162	C(Me)2CH2OMe	3-thienyl-N(Me)	C ₂₆ H ₃₂ N ₂ O ₃ S ₂
269163	C(Me)2CO2Me	3-thienyl-N(Me)	C ₂₆ H ₃₀ N ₂ O ₄ S ₂

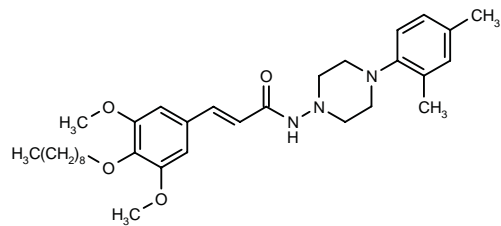
SOURCES – Tosoh; Yoshitomi.

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1. Tokunaga, T. et al. (The Green Cross Corp.;Tosoh Corp.) *Novel thiocarbamic acid derivs*. JP 98251224, WO 9830539.

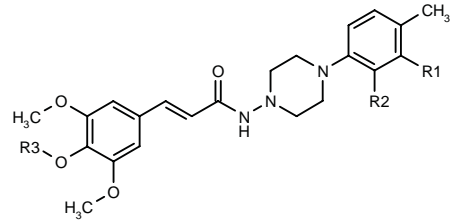
269386

3-(3,5-Dimethoxy-4-nonyloxyphenyl)-*N*-[4-(2,4-dimethylphenyl)piperazin-1-yl]-2(*E*)-propenamide



C32 H47 N3 O4; Mol wt: 537.7403

ACTION – Hypolipidemic and antiatherosclerotic agent with ACAT-inhibitory activity (IC₅₀ = 19 nM using enzyme from rat hepatic microsomes), shown to inhibit cholesterol accumulation *in vitro* in macrophages (IC₅₀ = 160 nM). *In vivo*, it was found to inhibit the increase in plasma cholesterol levels in rats fed a diet supplemented with 1.5% cholesterol (91% inhibition when administered mixed with the diet at 0.02%). A representative compound from a series of phenylpropenone derivatives, wherein the following are also included:



Compound	R1	R2	R3	Formula
269387	Me	H	C7H15	C ₃₀ H ₄₃ N ₃ O ₄
269388	Me	H	C8H17	C ₃₁ H ₄₅ N ₃ O ₄
269389	H	Me	C10H21	C ₃₃ H ₄₉ N ₃ O ₄
269390	H	Me	CH2Ph	C ₃₀ H ₃₅ N ₃ O ₄

SOURCE – Yakult Honsha.

REFERENCES

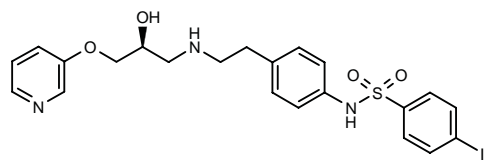
1. Sawada, H. et al. (Yakult Honsha Co., Ltd.) *Phenylpropenone cpds. and medicines containing them*. JP 98245357.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

L-749372

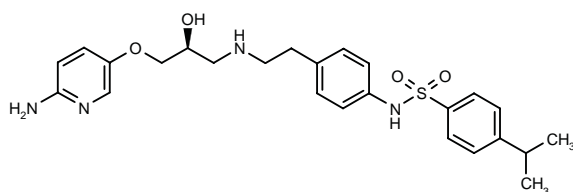
267918

N-[4-[2-[2(*S*)-Hydroxy-3-(pyridin-3-yloxy)propylamino]-ethyl]phenyl]-4-iodobenzenesulfonamide



C22 H24 I N3 O4 S; Mol wt: 553.4146

ACTION – Potent and selective partial human β_3 -adenoceptor agonist (EC₅₀ = 3.6 nM for stimulation of adenylyl cyclase in CHO cells; 33% activation relative to isoproterenol), with 270- and 30-fold selectivity relative to binding to β_1 - (IC₅₀ = 1000 nM) and β_2 -adrenoceptors (IC₅₀ = 110 nM), respectively. Compound stimulated lipolysis in rhesus monkeys with an ED₅₀ of 2 mg/kg i.v., without affecting heart rate. It exhibited good oral bioavailability in dogs (41%). Potentially useful for the treatment of obesity. Another compound from this series of 3-pyridyloxypropanolamines is:



L-750355 [267919]: C25 H32 N4 O4 S

SOURCE – Merck & Co.

REFERENCES

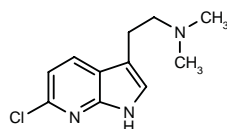
1. Fisher, M.H. et al. (Merck & Co., Inc.) *Substd. phenyl sulfonamides as selective β_3 agonists for the treatment of diabetes and obesity*. CA 2114712, EP 611003, JP 95010827, US 5451677, WO 9418161.

2. Weber, A.E. et al. 3-Pyridyloxypropanolamine agonists of the β_3 adrenergic receptor with improved pharmacokinetic properties. *Bioorg Med Chem Lett* 1998, 8(16): 2111.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

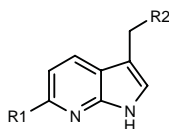
269513

N-[2-(6-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-*N,N*-dimethylamine



C11 H14 Cl N3; Mol wt: 223.7056

ACTION – Nicotinic acetylcholine receptor ligand for the treatment of addictive disorders such as tobacco addiction, as well as neurological and CNS disorders such as Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, anxiety, obesity, Tourette's syndrome and ulcerative colitis. A representative compound from a series of specifically claimed azaindole-ethylamine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
269514	Cl	CH ₂ NHMe	C ₁₀ H ₁₂ ClN ₃
269515	H	2-pyrrolidinyl	C ₁₂ H ₁₅ N ₃
269516	H	1-Me-2-pyrrolidinyl	C ₁₃ H ₁₇ N ₃
269517	H	CH ₂ N(Me) ₂	C ₁₁ H ₁₅ N ₃
269518	H	CH ₂ NHMe	C ₁₀ H ₁₃ N ₃
269519	H	CH ₂ NH ₂	C ₉ H ₁₁ N ₃
269520	H	1-Pip-CH ₂	C ₁₄ H ₁₉ N ₃

SOURCE – Pfizer.

REFERENCES

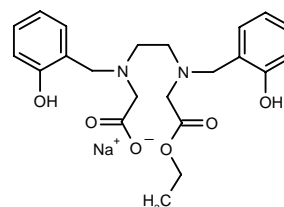
1. Nagel, A.A. (Pfizer Inc.) *Azaindole-ethylamine derivs. as nicotinic acetylcholine receptor binding agents*. EP 870768.

CGP-75254A*

268981

260268 (as free acid)

2-[N-[2-[N-(Ethoxycarbonylmethyl)-N-(2-hydroxybenzyl)-amino]ethyl]-N-(2-hydroxybenzyl)amino]acetic acid sodium salt



C₂₂ H₂₇ N₂ Na O₆; Mol wt: 438.4533

ACTION – Iron chelator, a monoethyl ester of HBED with an affinity for iron lower than that of HBED but at least as high as that of most orally active iron chelators. *In vitro* Caco-2 cell permeability and *in vivo* results in marmosets indicated high oral bioavailability for the compound. It does not act as a prodrug of HBED but is able to chelate iron by itself.

SOURCE – Novartis.

REFERENCES

1. Spanka, C. and Bühlmyer, P. (Ciba-Geigy AG) *N,N'*-Di(2-hydroxybenzyl)ethylenediamine-*N,N'*-diacetic acid derivs. WO 9744313.

2. Lowther, N. et al. *Caco-2 cell permeability of a new (hydroxybenzyl)ethylenediamine oral iron chelator: Correlation with physicochemical properties and oral activity.* J Pharm Sci 1998, 87(9): 1041.

*Identified compound **260268** (see **259038**) Drug Data Report 1998, 020(03): 0278.

DIAGNOSTIC AGENTS

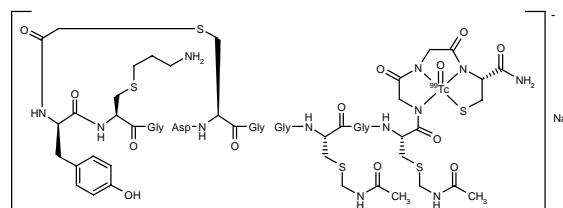
ACUTECT™

209213

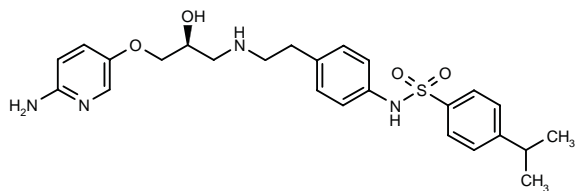
Sodium hydrogen [N-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinyl-glycyl-L-aspartyl-L-cysteinyl-glycyl-S-(acetamidomethyl)-L-cysteinyl-glycyl-S-(acetamidomethyl)-L-cysteinyl-glycyl-L-cysteinamide cyclic(1-5)-sulfidato(5-)-N¹¹,N¹²,N¹³,S¹³]-oxo^{[99mTc]technetate(V)}

Technetium (^{99m}Tc) apcitide (Prop INN)

[^{99m}Tc]-P280



C51 H73 N17 Na O20 S5 Tc: Mol wt: 1526.5570



L-750355 [267919]: C25 H32 N4 O4 S

SOURCE – Merck & Co.

REFERENCES

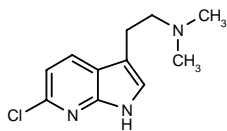
1. Fisher, M.H. et al. (Merck & Co., Inc.) *Subst. phenyl sulfonamides as selective β_3 agonists for the treatment of diabetes and obesity*. CA 2114712, EP 611003, JP 95010827, US 5451677, WO 9418161.

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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

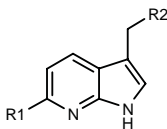
269513

N-[2-(6-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-*N,N*-dimethylamine



C11 H14 Cl N3; Mol wt: 223.7056

ACTION – Nicotinic acetylcholine receptor ligand for the treatment of addictive disorders such as tobacco addiction, as well as neurological and CNS disorders such as Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, anxiety, obesity, Tourette's syndrome and ulcerative colitis. A representative compound from a series of specifically claimed azaindo-ethylamine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
269514	Cl	CH2NHMe	C ₁₀ H ₁₂ ClN ₃
269515	H	2-pyrrolidinyl	C ₁₂ H ₁₅ N ₃
269516	H	1-Me-2-pyrrolidinyl	C ₁₃ H ₁₇ N ₃
269517	H	CH2N(Me)2	C ₁₁ H ₁₅ N ₃
269518	H	CH2NHMe	C ₁₀ H ₁₃ N ₃
269519	H	CH2NH2	C ₉ H ₁₁ N ₃
269520	H	1-Pip-CH2	C ₁₄ H ₁₉ N ₃

SOURCE – Pfizer.

REFERENCES

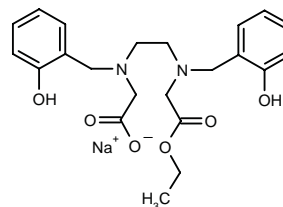
1. Nagel, A.A. (Pfizer Inc.) *Azaindo-ethylamine derivs. as nicotinic acetylcholine receptor binding agents*. EP 870768.

CGP-75254A*

268981

260268 (as free acid)

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C22 H27 N2 Na O6; Mol wt: 438.4533

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SOURCE – Novartis.

REFERENCES

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*Identified compound **260268** (see **259038**) Drug Data Report 1998, 020(03): 0278.

DIAGNOSTIC AGENTS

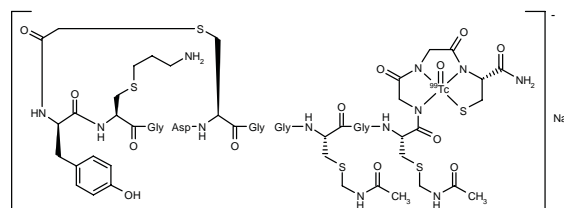
ACUTECT™

209213

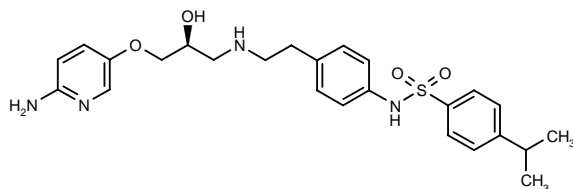
Sodium hydrogen [*N*-(mercaptoacetyl)-D-tyrosyl-*S*-(3-aminopropyl)-L-cysteinyl-glycyl-L-aspartyl-L-cysteinyl-glycyl-*S*-(acetamidomethyl)-L-cysteinyl-glycyl-*S*-(acetamidomethyl)-L-cysteinyl-glycyl-glycyl-L-cysteinamide cyclic(1-5)-sulfidato(5-)-*N*¹¹,*N*¹²,*N*¹³,*S*¹³]-oxo[^{99m}Tc]technetate(V)

Technetium (^{99m}Tc) apcitide (Prop INN)

[^{99m}Tc]-P280



C51 H73 N17 Na O20 S5 Tc; Mol wt: 1526.5570



L-750355 [267919]: C25 H32 N4 O4 S

SOURCE – Merck & Co.

REFERENCES

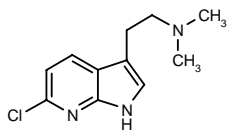
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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

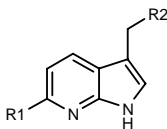
269513

N-[2-(6-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-*N,N*-dimethylamine



C11 H14 Cl N3; Mol wt: 223.7056

ACTION – Nicotinic acetylcholine receptor ligand for the treatment of addictive disorders such as tobacco addiction, as well as neurological and CNS disorders such as Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, anxiety, obesity, Tourette's syndrome and ulcerative colitis. A representative compound from a series of specifically claimed azaindole-ethylamine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
269514	Cl	CH2NHMe	C ₁₀ H ₁₂ ClN ₃
269515	H	2-pyrrolidinyl	C ₁₂ H ₁₅ N ₃
269516	H	1-Me-2-pyrrolidinyl	C ₁₃ H ₁₇ N ₃
269517	H	CH2N(Me)2	C ₁₁ H ₁₅ N ₃
269518	H	CH2NHMe	C ₁₀ H ₁₃ N ₃
269519	H	CH2NH2	C ₉ H ₁₁ N ₃
269520	H	1-Pip-CH2	C ₁₄ H ₁₉ N ₃

SOURCE – Pfizer.

REFERENCES

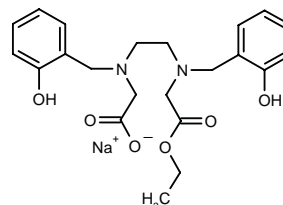
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CGP-75254A*

268981

260268 (as free acid)

2-[*N*-[2-[*N*-(Ethoxycarbonylmethyl)-*N*-(2-hydroxybenzyl)-amino]ethyl]-*N*-(2-hydroxybenzyl)amino]acetic acid sodium salt



C22 H27 N2 Na O6; Mol wt: 438.4533

ACTION – Iron chelator, a monoethyl ester of HBED with an affinity for iron lower than that of HBED but at least as high as that of most orally active iron chelators. *In vitro* Caco-2 cell permeability and *in vivo* results in marmosets indicated high oral bioavailability for the compound. It does not act as a prodrug of HBED but is able to chelate iron by itself.

SOURCE – Novartis.

REFERENCES

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2. Lowther, N. et al. *Caco-2 cell permeability of a new (hydroxybenzyl)ethylenediamine oral iron chelator: Correlation with physicochemical properties and oral activity*. J Pharm Sci 1998, 87(9): 1041.

*Identified compound **260268** (see **259038**) Drug Data Report 1998, 020(03): 0278.

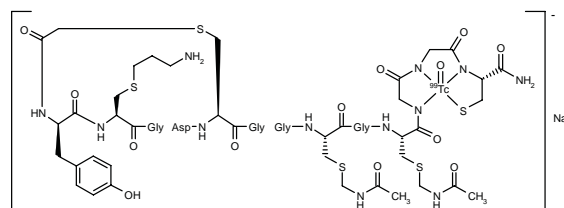
DIAGNOSTIC AGENTS

ACUTECT™

209213

Sodium hydrogen [*N*-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinyl-glycyl-L-aspartyl-L-cysteinyl-glycyl-S-(acetamidomethyl)-L-cysteinyl-glycyl-S-(acetamidomethyl)-L-cysteinyl-glycyl-glycyl-L-cysteinamide cyclic(1-5)-sulfidato(5-)-*N*¹¹,*N*¹²,*N*¹³,*S*¹³]-oxo[^{99m}Tc]technetate(V)

Technetium (^{99m}Tc) apcitide (Prop INN)
[^{99m}Tc]-P280



C51 H73 N17 Na O20 S5 Tc; Mol wt: 1526.5570

ACTION – Kit for the preparation of technetium (99mTc) apcptide, a peptide-based diagnostic radiopharmaceutical that targets acute blood clots in the lower extremities; the small-molecule synthetic peptide adheres to activated platelets.

INDICATION – Scintigraphic imaging of acute venous thrombosis in the lower extremities.

PRESENTATION – Each kit contains one vial containing a sterile, nonpyrogenic, freeze-dried mixture of bibapcptide, an apcptide dimer, stannous chloride dihydrate and sodium glucoheptonate dihydrate. When sterile, nonpyrogenic Sodium Pertechnetate Tc 99m Injection in 0.9% Sodium Chloride Injection, USP is added to the vial and heated, the bibapcptide is split and forms technetium (99mTc) apcptide.

PROPRIETARY NAME – *AcuTect* (US).

SOURCES – Diatide; Nycomed Amersham.

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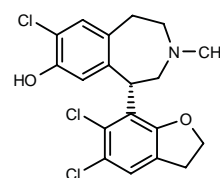
27. *Proposed international nonproprietary names (Prop. INN): List 78*. WHO Drug Inf 1997, 11(4): 292.

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NNC-22-0215*

203360

(+)-7-Chloro-1-(5,6-dichloro-2,3-dihydrobenzofuran-7-yl)-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine



C19 H18 Cl3 N O2; Mol wt: 398.7152

ACTION – High-affinity, selective, metabolically stable dopamine D₁ receptor antagonist, as demonstrated in binding studies (K_i = 0.3 nM for inhibition of [³H]-Sch-23390 binding in rat brain homogenates; K_i = 38 nM for inhibition of [³H]-spiperone binding [D₂]; K_i = 88 nM for inhibition of [³H]-ketanserin binding [5-HT₂]), originally developed as a potential antipsychotic agent. More recent studies in monkey brain indicated that [¹¹C]-labeled compound has potential as a radioligand in PET imaging of human brain D₁ receptors.

SOURCE – Novo Nordisk.

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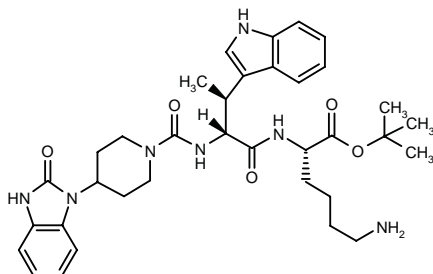
*Identified compound **203360** (see **200957**) Drug Data Report 1994, 016(02): 0136.

PHARMACOLOGICAL TOOLS

L-054522

268061

N-[4-(2-Oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-ylcarbonyl]-[3(*S*)-methyl]-*D*-tryptophyl-L-lysine *tert*-butyl ester



C35 H47 N7 O5; Mol wt: 645.8003

ACTION – Nonpeptide somatostatin sst2 receptor agonist with high affinity ($K_i = 0.01$ nM against [125 I]-somatostatin-28 binding in membranes from CHO-K1 cells expressing human sst2 receptors) and high selectivity (at least 3000-fold) versus other somatostatin receptor subtypes. Compound had full agonist activity, as determined by inhibition of forskolin-stimulated cAMP production in L cells cotransfected with sst2 receptors ($IC_{50} = 0.1$ nM). It inhibited growth hormone (GH) release from rat anterior pituitary cells ($IC_{50} = 0.05$ nM) and insulin and glucagon release from isolated mouse pancreatic islets ($IC_{50} = 12$ and 0.05 nM, respectively). *In vivo* in rats, it produced a rapid and sustained reduction in GH release when infused at $50 \mu\text{g/kg/h}$. Potentially useful as a tool to characterize the physiological and pathophysiological roles of sst2 receptors.

SOURCE – Merck & Co.

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